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ACTA RADIOLOGICA

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EDITA IUSSU SOCIETATUM RADIOLOGICARUM
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VOL. 41 JUNE 1954 FASC. 6

ROENTGENOLOGIC STUDIES OF THE SPHINCTER MECHANISM OF THE CAVAL AND PULMONARY VEINS

by

Sven Roland Kjellberg and *Sten-Erik Olsson*

Angiocardiography is a method which can provide valuable information, not only concerning the internal anatomy of the heart and blood vessels, but also to some extent about the way in which they function. Obviously, due consideration must be paid to its sources of error.

In angiocardiography in children, we have often been struck by the fact that the width of the lumen in the extremities of the caval and pulmonary veins undergoes considerable variations. We felt that this might prove to be an important link in the working mechanism of the heart and considered it of interest to make a closer analysis of this detail. The phenomenon might have been an effect of the strongly hypertonic and irritating contrast media and for this reason we decided to make a comparative investigation in animals, using a contrast medium free from such effects.

Material

Dogs were used as the experimental animals, their heart rate being broadly the same as in man. Six healthy dogs of ages ranging between four months and two years were used. The human material consisted of ten children, aged between six months and fifteen years, who for some reason had undergone intravenous angiocardiography instead of, or as a complement to, selective angiocardiography. These children suffered from various forms of congenital heart disease and do not, therefore, represent a normal material. We nevertheless consider that a comparison is not entirely unjustified; the heart diseases in question affected neither the caval nor the pulmonary veins and, owing to the risks associated with angiocardiography, it is difficult to assemble a normal series.

Submitted for publication, Dec. 7, 1953.

From the Roentgen Department (Director: S. R. KJELLBERG) of the Paediatric Clinic of Karolinska Sjukhuset, and the Roentgen Department (Director: S. E. OLSSON) of the Royal Veterinary College, Stockholm, Sweden.

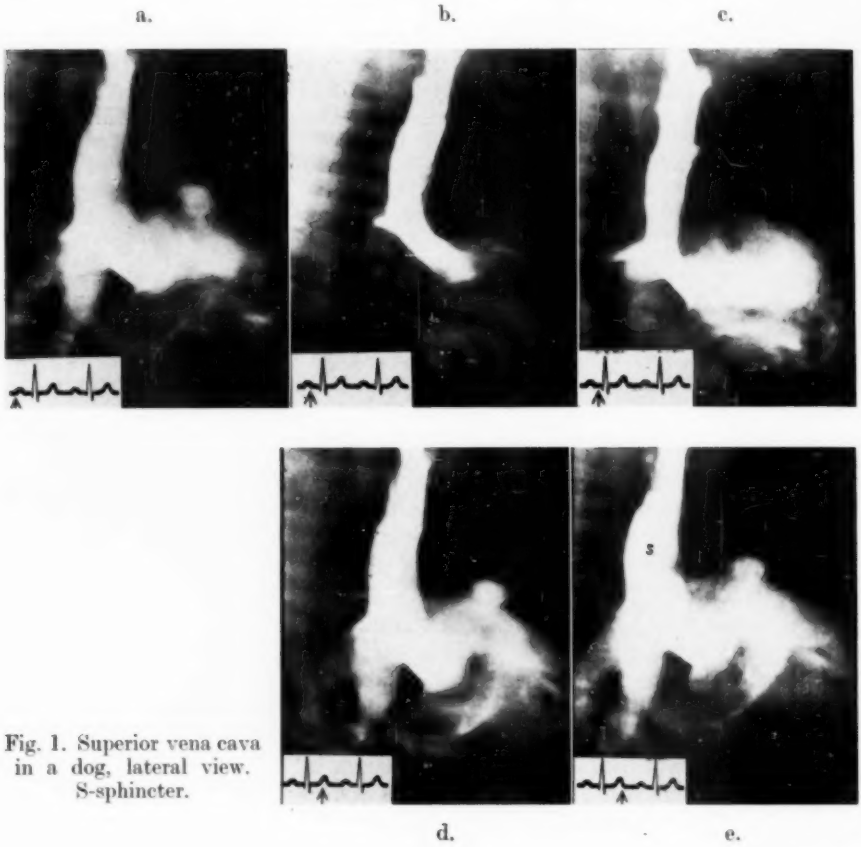


Fig. 1. Superior vena cava in a dog, lateral view. S-sphincter.

Methods

All the examinations in the dogs were made under general intravenous anaesthesia. Each animal was usually given two injections of the contrast medium, at an interval of 20 to 30 minutes. In two cases, the examination was repeated after a lapse of two weeks.

In order to study the caval veins, no. 8—10 Cournand catheters were inserted into the jugular and femoral veins. The contrast medium was injected alternately into the inferior and superior vena cava, and in some cases simultaneously into both veins as well. For the study of the pulmonary veins, the contrast medium was injected through catheters of the same calibre, the tip being placed in the main trunk of the pulmonary artery or in the upper part of the right ventricle.

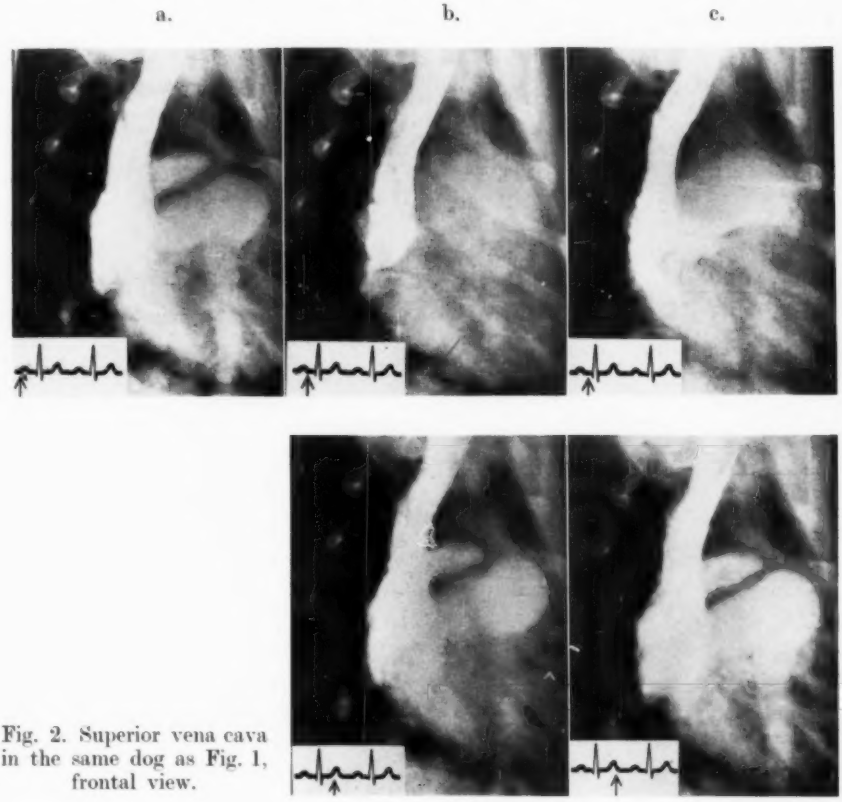


Fig. 2. Superior vena cava in the same dog as Fig. 1, frontal view.

In three cases, a 70 per cent solution of the Perabrodil-Diodrast group (Umbradil, Astra) was used. In order to ascertain whether this strongly irritating, hypertonic contrast medium had a specific effect, a comparative examination was made with thorotrast on five occasions. Each injection consisted of 20—70 ml of contrast medium, depending on the size of the animal. This corresponds to 2—3 times the quantity per kg of body weight injected in children. Such a large quantity was chosen in order to permit a study of a larger number of cardiac cycles. The quantity of contrast medium per time unit was, however, the same in both categories.

In most cases, the injection was made with an automatic pressure syringe (Gidlund's principle) which allows the rate and pressure of injection to be precisely determined in advance. The syringe was provided with a thermostat, so that the contrast medium was injected at blood heat.

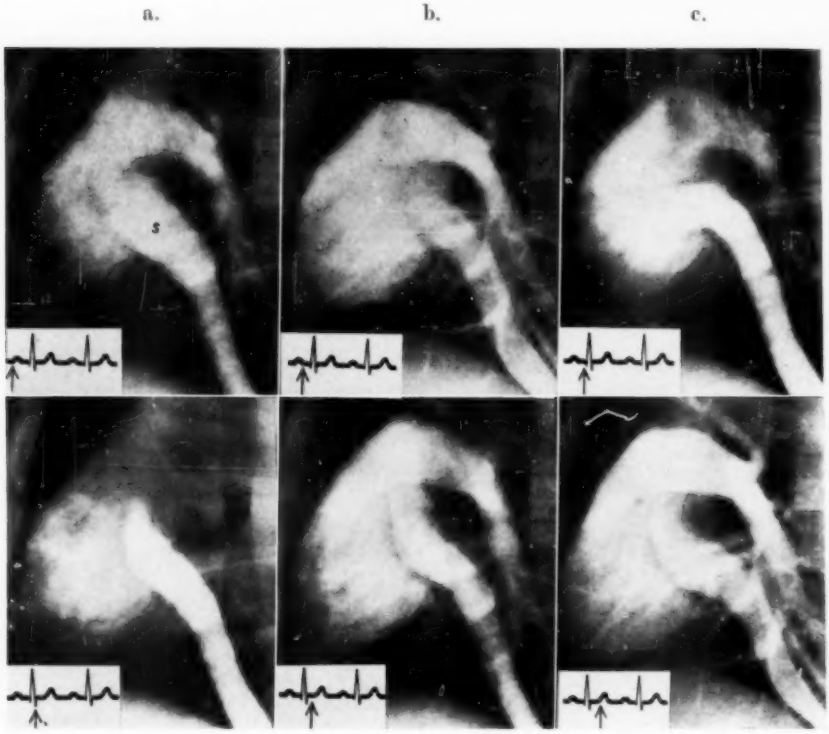
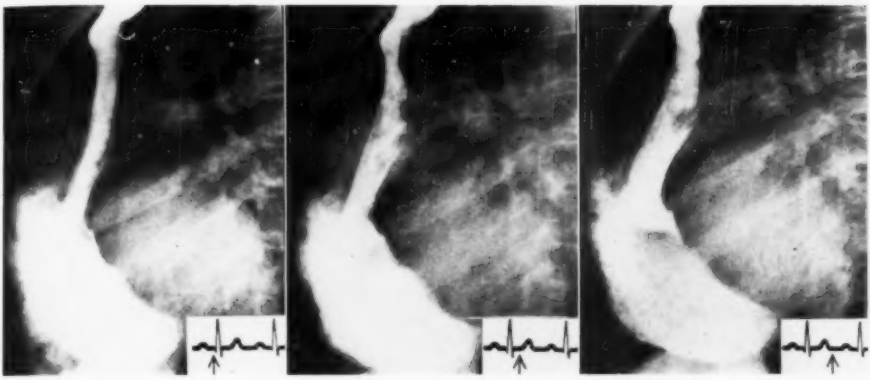


Fig. 3. Inferior vena cava in a dog, lateral view. S-sphincter.

The syringe was connected to the serial changer and was always adjusted so that the latter started simultaneously with the beginning of the injection. The roll-film serial changer (Gidlund's principle) is constructed in two planes at right angles to each other, the maximum size of each film being 30 × 30 cm. Both frontal and lateral projections were used in every case. The exposures were made simultaneously in both planes, the rate varying between 8 and 12 per second, depending on the size and heart rate of the animal. Because of the depth of the thorax in the dog, the intensity was not the same for both projections. In the frontal projection we used 350 mA, and in the lateral 200 mA. The exposure time was 0.004 second for the five smallest dogs, and 0.014 second for the sixth. The voltage varied between 80 and 120 kV, according to the size of the animal. We used a three-phase roentgen apparatus equipped with a contactor with thyratron tubes.



a. b. c.

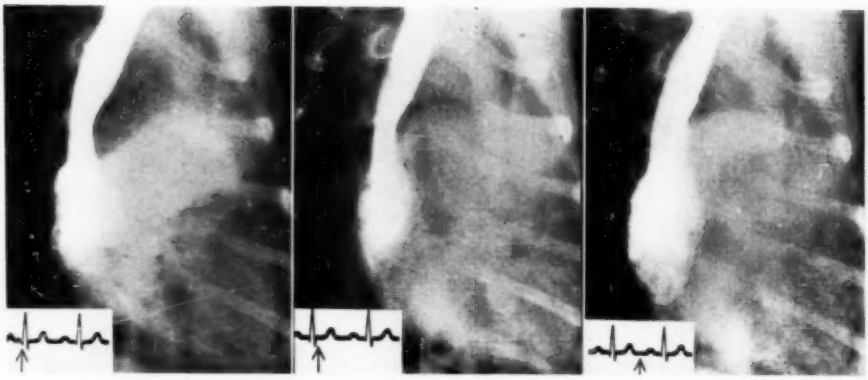
Fig. 4. Superior vena cava in a child, lateral view.

In intravenous angiocardiography in children, the contrast medium was injected either manually into a vein of the arm or leg, or with a pressure syringe through a Cournand catheter inserted distally into the superior or inferior vena cava. The contrast medium was a 70 per cent solution of the Perabrodil-Diodrast group or of Urokon. The quantity injected was 1.2 cc per kg of body weight. Serial roentgenography as already described was employed, except that the same milliamperage was used for both tubes, *i. e.* 350 mA.

In both the animals and the children, the position of the exposures in the cardiac cycle was recorded simultaneously with lead II of the ECG. This also served as a check on the ECG being normal during the periods of interest for the study of the sphincter mechanism — the heart continued to function in the normal way.

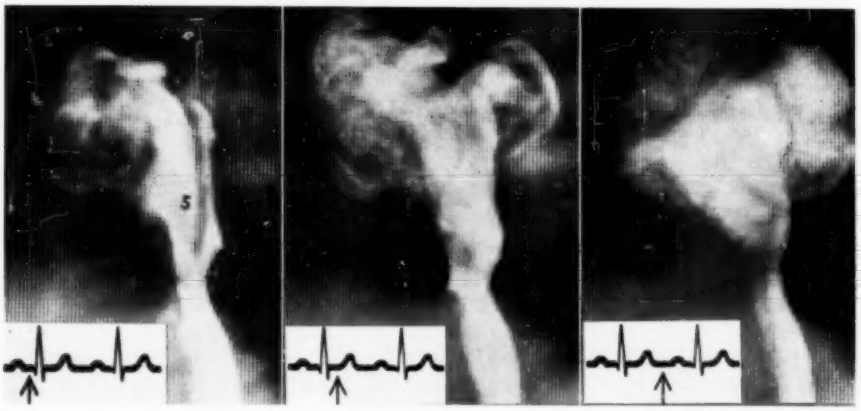
Results

It was evident from all the animal experiments that the extremities of the inferior and superior venae cavae performed a movement synchronous with the action of the heart. In the beginning of auricular systole, a rapid contraction took place in the lower 2—3 centimeters of the superior vena cava and in the upper 1—2 centimeters of the inferior vena cava. As shown in Figs. 1—6, the contraction started during the rising limb of the P wave, or at the level of its peak, and reached a maximum after 0.04—0.06 second. The contraction persisted unchanged for about 0.1 second; a slow relaxation then set in. The vessel did not, as a rule, attain its maximal width until after a further 0.1—0.2 second, shortly



a. b. c.

Fig. 5. Superior vena cava in a dog, frontal view.



a. b. c.

Fig. 6. Inferior vena cava in a child, lateral view. S-sphincter.

after the end of the T wave, and presumably in connexion with the opening of the auriculo-ventricular valves. The contraction occurred circularly. As seen in Table 1, the difference between the maximum and minimum width of the vessel, measured 3—4 mm distally to its emptying into the auricle, amounted to about 40 per cent. The contraction thus brought about a decrease in the cross-section area of the vessel of about 70 per cent. No reflux into the contralateral vena cava, however, was observed in any of the cases.

Table 1

The Difference Between the Maximum and Minimum Width of the Caval Veins

	Sup. v. cav.			Inf. v. cav.		
	Max. width in mm	Min. width in mm	Decrease of width in %	Max. width in mm	Min. width in mm	Decrease of width in %
Dog 1	14	8.5	39			
Dog 2	12	7	41.5	16	9	44
Dog 3	13	8.5	35	16	10	37.5
Dog 4	13	8	38	17	9.5	44
Dog 5	15	9	40	19	12	37
Dog 6	14	8	43	18	11	39
L. C. 6 yrs	23	14	39			
B. H. 4 yrs				28	16	42.5
R. T. 8 yrs	25	15	40	20	12	40
M. N. 14 yrs	27	16	41			
N. S. 3 yrs	17	9.5	44			

The conditions were identical in the pulmonary veins (Figs. 7—8). Since these vessels often run in different planes, a calculation of the lumen can be made only on the vessel or vessels running parallel to the plane of the film. Measurements could be made therefore only on six occasions. A distinct contraction of the vessel was observed in a segment about 2 cm long. The mean maximal decrease in the area amounted to 70 per cent. This change in the lumen was also apparent as a change in the density of the contrast medium. No difference could be noted in the final results by using the different contrast media.

Discussion

The manner of contraction of the extremities of the caval veins as well as of the pulmonary veins, suggests a valvular mechanism. Its task would be to prevent or hamper the regurgitation of blood to the veins in connexion with auricular systole. Whether or not such a mechanism exists has been the subject of much discussion in the literature. Some authors, for example, BURCH, LIND and WEGELIUS, and PRINZMETAL et al., consider that it does exist, whereas others are of the opposite opinion. Thus, WIGGERS writes on page 583:

"No effective valvular structures have been found at the junctions of the large veins and the atria, but regurgitation does not appear to occur during atrial contraction. Anatomists have suggested that the contraction of circular bands acts to constrict these orifices; but experimental evidence indicates that they remain patent. The physical forces

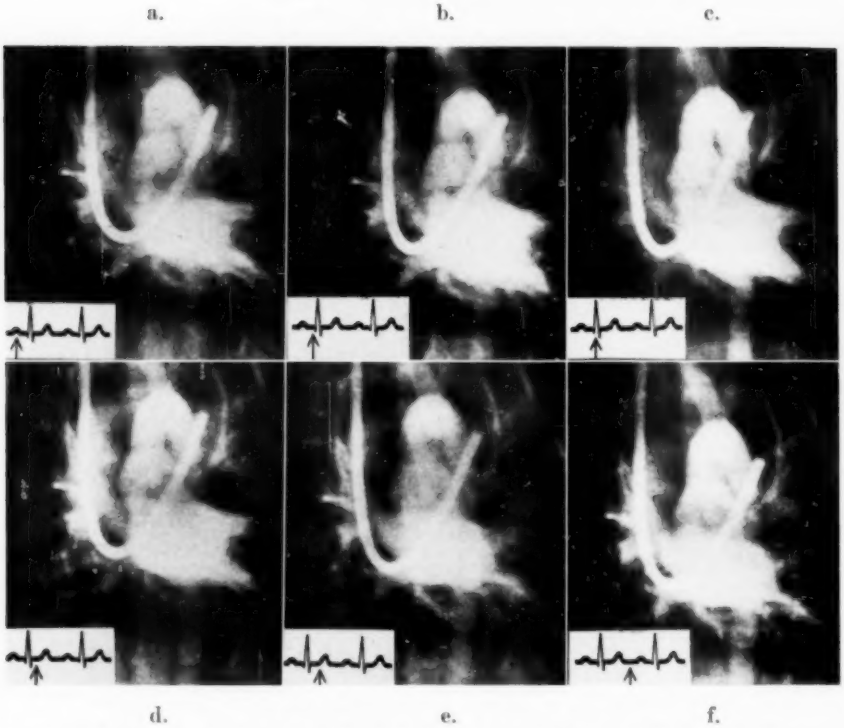
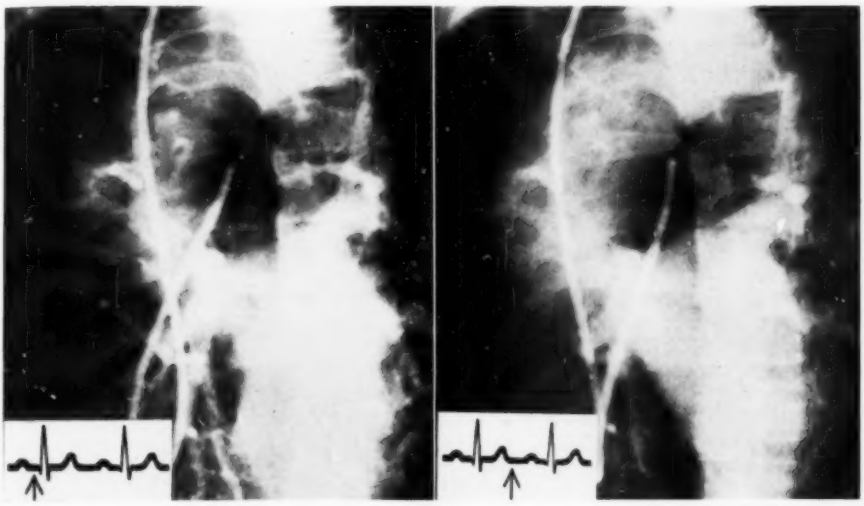


Fig. 7. Pulmonary vein in a dog, frontal view; the vein being studied lies in the curve of the catheter.

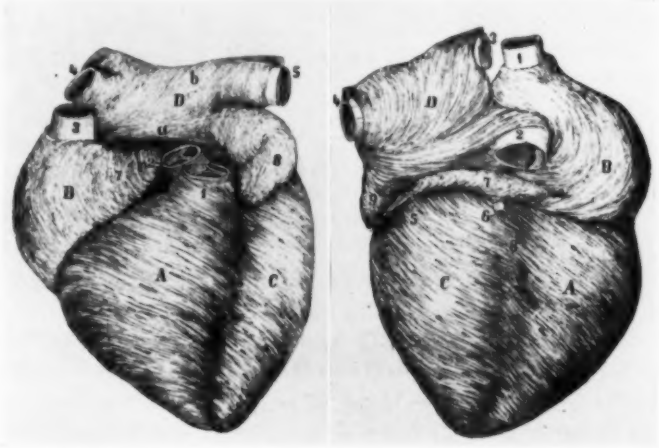
which prevent regurgitation are (a) the necessity of stopping the onflowing blood before the stream can be reversed, (b) the fact that pressure is lower in the ventricles than in the veins so that the atria tend to empty in the direction of least resistance, (c) the peristaltic mode of contraction which favours emptying towards the ventricles, and (d) the emptying of the atria during early ventricular diastole so that they contain but a small quantity of blood when the atria contract."

According to most anatomic descriptions, the auricular muscles in man are composed of two layers. One is superficial and is common to both auricles. The other and deeper layer is separate for each auricle and has a particular anatomic structure. It consists of both looped and annular fibres. The annular fibres encircle not only the auricles but also those segments of the caval veins, pulmonary veins and coronary sinus emptying into the auricles. In the case of the latter, the fibres originate in the left auricle (Fig. 9). According to RAUBER and KOPSCH, these fibres continue for a short distance distally along the veins. SPALTEHOLTZ stated that the



a. b.

Fig. 8. Pulmonary vein in a child; the vein being studied lies opposite the aorta.



a. b.

Fig. 9. A. Right ventricle, B. right auricle, C. left ventricle, D. left auricle. a. 1. Pulmonary artery, 2. aorta, 3. superior vena cava, 4. right pulmonary veins, 5. left pulmonary veins, 7. right auricular appendage, 8. left auricular appendage. b. 1. Superior vena cava, 2. inferior vena cava, 3. right pulmonary veins, 4. left pulmonary veins, 7. coronary sinus, 9. left auricular appendage (From RAUBER and KOPSCH: Lehrbuch der Anatomie des Menschen).

annular fibres around the pulmonary veins extend as far as the reflection of the pericardium onto the vessels.

The conditions are similar in mammals. However, according to LECHNER, both the arrangement of the muscle fibres and their extent along the vessels vary with the species of animal. In his opinion, their range along the caval veins is intimately associated with the development of the sinus venosus. As a rule, the muscles extend further along the superior vena cava than along the inferior. He stated:

"An den ins rechte Atrium mündenden Venen reicht die Herzmuskulatur bis zu den Grenzen des ehemaligen Sinusraumes und ist daher desto weiter reichend, je mehr von diesem in die Venenwand einbezogen worden ist und umgekehrt. Ja, es ist förmlich die jetzige Muskelgrenze ein Merkpunkt für die Abgrenzung des ehemaligen Sinusraumes (rein äusserlich betrachtet). Am meisten ist von diesem noch in der Vena cava cran. sin. bzw. in der Vena azygos sin. erkennbar, daher reicht bei deren Vorhandensein die Herzmuskulatur am weitesten peripher. Bei anderen Säugetieren ist der ehemalige Sinusraum Muskeltrichter um das Mündungsstuch der Vena cava cran. dextr. geworden mit oder ohne Einbeziehung des Abganges der V. azygos dextr. Am wenigsten überdeckt von Herzmuskulatur wird die hintere Hohlvene."

There are also considerable variations in the extent of the muscle fibres along the pulmonary veins. According to the same author, they reach far into the lungs in the lowest mammals, their termination becoming increasing central the higher the developmental series. He wrote:

"Am linken Atrium wird die bei den niedersten Säugern einzig und noch extrakardial vorhandene Aufteilung des Lungenvenenstammes als Muskeltrichter in das Atrium einbezogen und so die Grundlage des Fasc. interauricularis verticalis. Er liefert dann die Herzmuskulatur der Lungenvenen. Daher ist bei den niederen Säugerklassen die Herzmuskulatur noch weit in die Lungen zu verfolgen (langer Muskeltrichter als gemeinsamer Lungenvenenstamm bis zur Aufteilung in die Lunge selbst), während bei höheren Säugerklassen immer mehr von diesem Muskeltrichter ins linke Atrium aufgeht, so dass schliesslich von ihm nur mehr Trennungsbündel zwischen den einzelnen Ästen seines ursprünglichen einheitlichen Stammes übrigbleiben, die bei den Primaten nur wenig weit peripher reichen. Belanglos ist für dieses Verhalten der Verlauf des Fasc. interaur. vert. und auch die Anzahl der Lungenvenen."

In the opinion of ELLENBERGER and BAUM, the muscle fibres passing from the heart to the pulmonary veins have an annular arrangement; their contraction prevents regurgitation of the blood in auricular systole. They wrote:

"Sie (venae pulmonales) folgen ..... im allgemeinen den Ventralwand der grösseren Bronchen und sind klappenlos und anfänglich (in zirkulärer Anordnung) mit Fortsetzungen der Herzmuskulatur versehen, durch deren Kontraktion bei der Vorkammersystole der Rückfluss des Blutes aus dem Atrium verhindert wird (MARTIN)."

It is evident from this description that there are satisfactory prerequisites for muscular changes in the lumen of the extremities of the veins in question. The association of the muscle fibres with the auricular

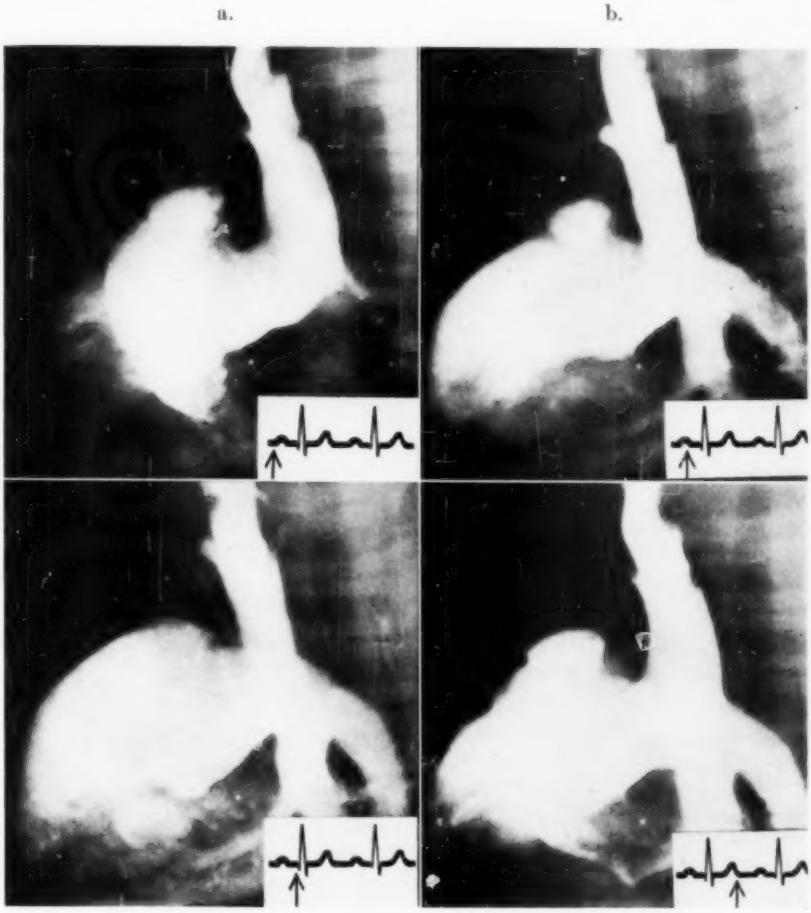


Fig. 10. Superior vena cava in a dog, lateral view.

muscles also makes their coordination highly probable. The site at which we observed vascular contractions is in good agreement with that of the annular fibres described. We therefore consider that there are strong grounds for concluding that it is these fibres which bring about the local contraction of the veins. Further support is afforded by the fact that no changes of this nature occurred in the lumen of other parts of the veins.

Our investigations possibly indicate a method for determining the extent of these fibres along the trunks of the vessels. Judged from the

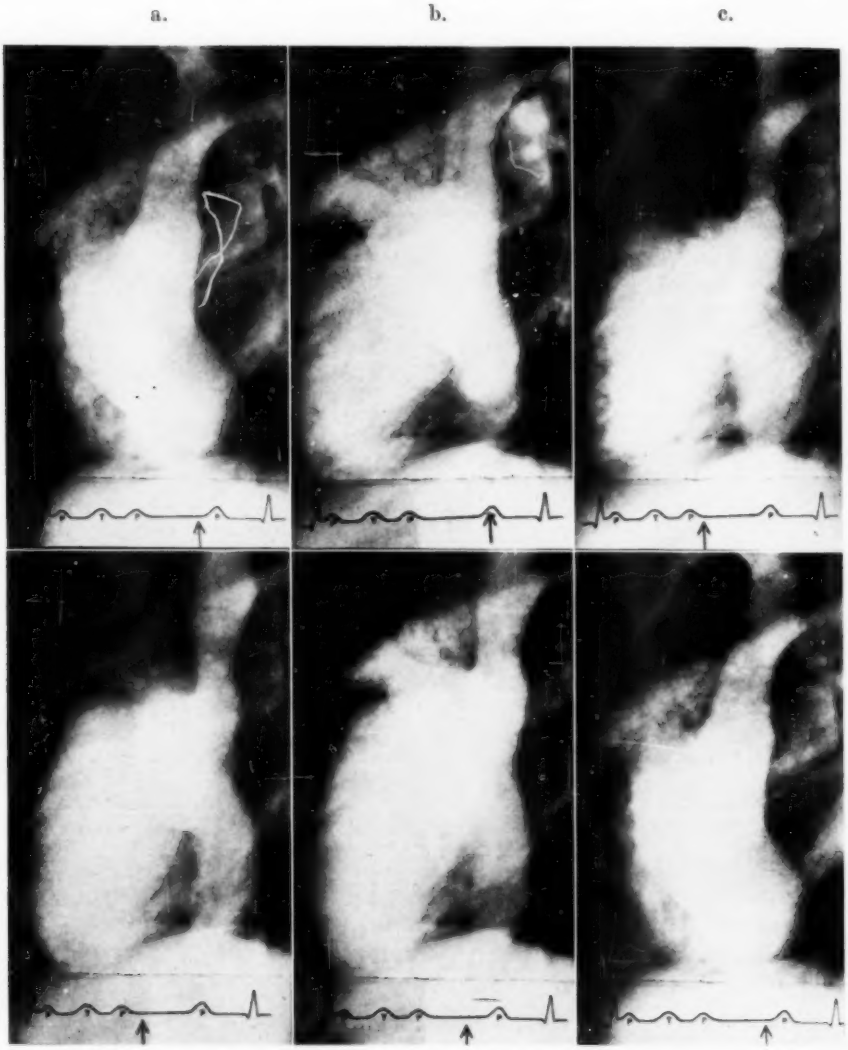


Fig. 11. Superior vena cava in a child with complete heart block, lateral view.

roentgenograms, they extend considerably further along the superior vena cava than along the inferior. In both dogs and children, we observed a contraction in a 2—3 cm length of the superior vena cava, approximately

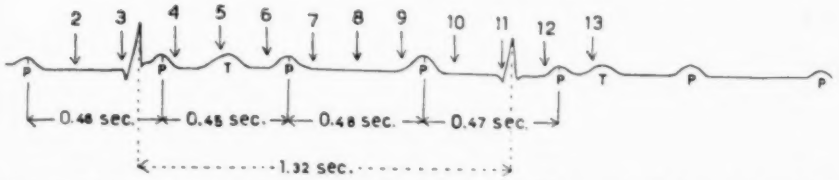


Fig. 12. ECG from the child with complete heart block. The numbers show the position in the cardiac cycle at which the exposures are made.

at the level of the emptying of the azygos vein (see Figs. 10—12). In the inferior vena cava, on the contrary, it was confined to a 1—2 cm portion (Fig. 13). This difference may explain, wholly or in part, why impaired blood flow from the right side of the heart is first manifested in the lower part of the body, particularly in the liver. This applies both in man and in animals.

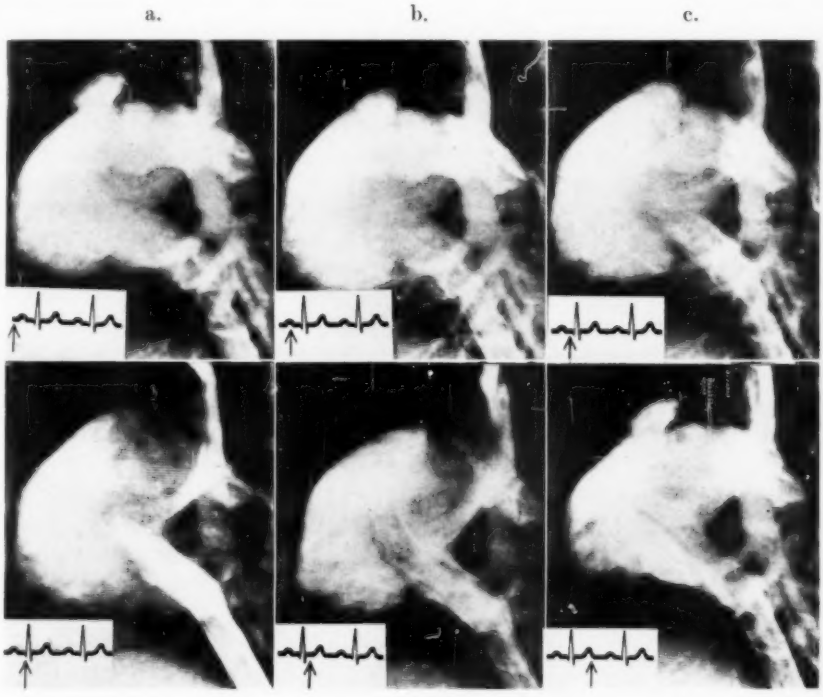


Fig. 13. Inferior vena cava in a dog, lateral view.

Our results also show that the contraction occurs synchronously with auricular systole. Its onset is extremely rapid and it is practically complete as soon as the beginning of mechanical systole; it remains unchanged throughout systole, relatively slow relaxation then occurring. We consider these facts to be a strong argument in favour of the sphincter function of the muscle fibres described, their task being (a) to prevent regurgitation of blood to the veins in connexion with auricular systole; (b) to slow down the blood flow in the beginning of auricular diastole so that the filling of the auricle is adapted to the relaxation.

The occurrence of such a sphincter mechanism in the caval veins has recently been described by HEDMAN, LIND and WEGELIUS. With regard to the inferior vena cava, they came, however, to the somewhat surprising conclusion that this vessel reacts inversely to the superior vena cava. Thus, it becomes dilated when the superior vena cava contracts. They stated: "In contrast to the superior caval vein the proximal part becomes dilated in atrial systole and thin in diastole when the passage into the atrium is free." A possible explanation is that their roentgenograms were taken in oblique projections. In both the dog and man, the inferior vena cava is so situated, and its course in its proximal part is so curved that the short sphincter area cannot be studied to advantage other than in true frontal and lateral projections.

The observation made by PRINZMETAL et al. that such a sphincter mechanism occurs in the caval but not in the pulmonary veins, is in contradiction to our findings. A possible explanation is that their studies were made under the unphysiologic conditions of an open thorax.

We wished to obtain, if possible, further evidence of our conception of the importance of the sphincter mechanism. We therefore studied the conditions in three cases in which there was considerable difficulty in emptying the right side of the heart. The caval veins were distinctly dilated in all three patients. During the injection — which was made distally into the superior or inferior vena cava — a strong reflux of the contrast medium into the contralateral vena cava was observed during auricular systole. During this phase, a slight contraction took place in the lumen of the extremity, but it was less marked than that described earlier. Pressure measurements in the caval veins were also made in two of these cases. The marked rise in pressure during auricular systole may presumably be attributed, at least in part, to an incompetence of the valvular mechanism in question. This, in conjunction with the strong reflux of contrast medium into the contralateral vena cava, indicates that factors other than those mentioned by WIGGERS exist. In other words, a valvular mechanism is present which, in normal cases, contributes to the propulsion of the blood in the correct direction during auricular systole.

In order to study experimentally the effect of such a valvular mech-

anism, we constructed an apparatus of the following principle (Fig. 14). To the wheel A is attached a heel, shaped to resemble the course of contraction of the sphincters. It serves to compress to the desired extent a thin-walled rubber tube, VC, corresponding to the vena cava. Distally to this sphincter mechanism, the pressure can be increased synchronously by means of a magnetic valve, M. If a continuous stream of fluid is allowed to flow through VC and the pressure is suddenly increased distally to the disconnected sphincter mechanism, S, a simultaneous rise in pressure occurs in VC. This is accompanied by vibrations in the wall of the tube and the fluid. If the extra pressure is removed, the pressure in VC returns to its original level. Otherwise, it remains at a higher level (Fig. 15 a). If S is started during a continuous flow through VC, the pressure curve recorded in Fig. 15 b is obtained. The compression was adjusted to result in constriction of a 1.5 cm portion of the tube to half its original diameter. It is evident from the curve that compression causes a distinct rise in pressure in VC with the simultaneous occurrence of certain vibrations. If the pressure

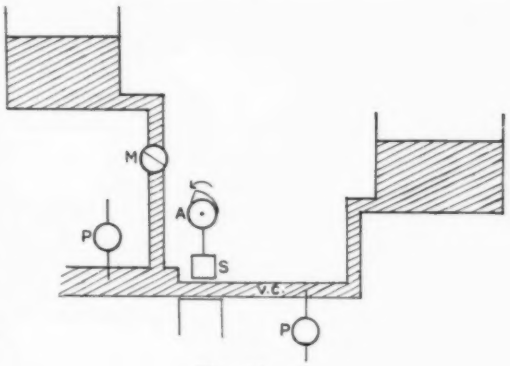


Fig. 14.

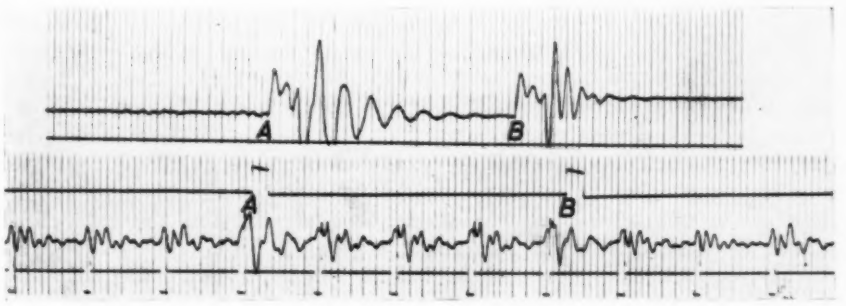


Fig. 15. Upper curve A: At A, sudden increase in pressure distal to the disconnected sphincter S. At B, sudden increase in pressure, remaining at the same level for some time. No sphincter working. Lower curve B: To the left: Constant flow and sphincter S working. Between A and B increased pressure distal to S, synchronized with the sphincter. After B no extra pressure distal to S.

distally to S — as already described — is increased synchronously, the pressure in VC does not rise above the earlier level (Fig. 15 b). If this curve is compared with a normal catheterization curve for the vena cava, it is found to bear a striking resemblance to it (Fig. 16).

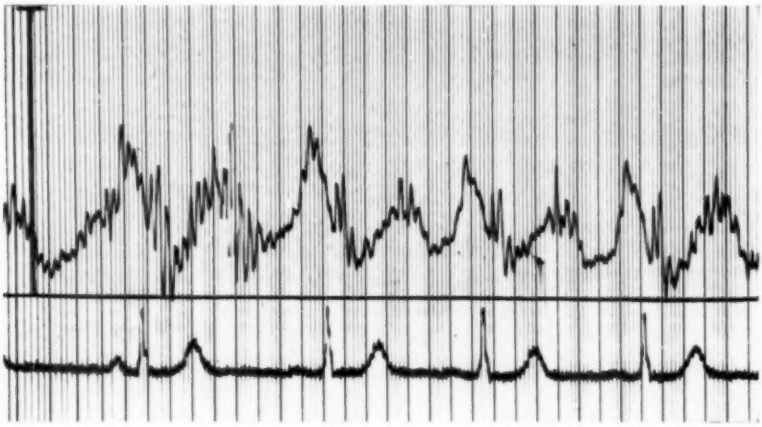


Fig. 16.

We are fully aware of the weaknesses of a comparison between the conditions *in vivo* and the results of such a mechanical procedure. The method nevertheless represents an attempt to isolate the different factors. The experiment may possibly afford some conception of the course of events. It would be largely the contractions of the sphincter mechanism that are reflected in the pressure curves for the caval and pulmonary veins recorded on catheterization of the heart. In view of the facts shown both by angiocardiography and pressure measurements, it seems reasonable to draw the following conclusions. A sphincter mechanism is present at the junction of the caval and pulmonary veins and the auricles. This sphincter mechanism presumably contributes to preventing regurgitation during auricular systole. It thereby facilitates the transport of the blood from the auricle to the ventricle and modifies the rate of the venous flow to the auricle in auricular systole.

SUMMARY

The authors have attempted by means of roentgenologic and experimental studies to confirm the presence of a sphincter mechanism in the extremities of both the caval and the pulmonary veins. Studies have also been made of the mode of action of this sphincter mechanism.

ZUSAMMENFASSUNG

Die Verf. haben mit Hilfe röntgenologischer und experimenteller Studien versucht, das Vorhandensein eines Sphinktermechanismus in den herznahen Abschnitten der V. cave sup. et inf. und der V. pulmonales zu bestätigen. Die Wirkungsweise dieses Sphinktermechanismus wurde ebenfalls studiert.

RÉSUMÉ

Les auteurs ont essayé de confirmer par des recherches radiologiques et expérimentales l'existence d'un mécanisme sphinctérien à l'extrémité des veines caves et pulmonaires. Ils ont aussi étudié le mode d'action de ce mécanisme sphinctérien.

REFERENCES

Burch, George: A Primer of Venous Pressure. Lea & Febiger, Philadelphia 1950.

Ellenberger and Baum: Handbuch der vergleichenden Anatomie der Haustiere, 18th Edition. Springer, Berlin 1943.

Hedman, C., Lind, J. and Wegelius, C.: Caval refluxes in angiocardiography and the dynamics of the right atrium. Brit. Heart. J. 15 (1953), 143.

Lechner, W.: Vorkammermuskulatur und grosse Herzvenen bei den Säugetieren. Zschr. Anat. u. Entw. 111 (1941—1942), 545.

Prinzmetal, M., Corday, E., Brill, I., Oblath, R. and Kruger, H. E.: The auricular arrhythmias. Thomas, Springfield, Ill. 1952.

Rauber and Kopsch: Lehrbuch und Atlas der Anatomie des Menschen, Thieme, Leipzig 1948.

Spalteholz, W.: Handatlas der Anatomie des Menschen, 14th Edition. Hirzel, Leipzig 1939.

Wiggers, Carl: Physiology in Health and Disease, Fifth Edition. Lea & Febiger, Philadelphia 1951.

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CALCIFIED INTERVERTEBRAL DISC IN CHILDREN AND ADULTS

by

S. Schorr and *E. Adler*

Calcification of the intervertebral disc in adults has been reported frequently since first described by CALVÉ and GALLAND in 1922 (6). SCHMORL (17) and RATHKE (14) found it relatively frequently in post-mortem examinations, and since its incidence increased with age, regarded it as a degenerative process. When such, clinical signs are rarely found (12).

Calcification of the disc affects the annulus fibrosus about ten times as often as it affects the nucleus pulposus (14, 3). SANDSTRÖM (16) pointed out that when the peripheral parts of the disc are involved, the calcification appears to be permanent. When the central parts of the disc are affected, the calcified deposits are more often reversible. These lesions are usually found in adults in the lumbar or lower thoracic spine.

In contrast with the calcified disc frequently found in adults is its rare occurrence in children. In 1945, WEENS found only five cases reported as occurring in childhood and added one case of his own (20). In these cases the lesions were situated in the cervical and upper thoracic spine, were associated with pain, and disappeared in a comparatively short period of time.

The purpose of this paper is to emphasize the distinct difference in the clinical and roentgenologic picture of the condition in children as compared with adults, and to present an additional case of calcified deposits in the intervertebral disc occurring in a child.

Case report. A healthy, normally developed eight-year-old boy fell in the bath tub on 23 April 1952. There were no immediate symptoms, but the following morning he awoke with severe pain in the neck. There was marked torticollis, with the head inclined to the right and complete limitation of movement of the head and neck. Treatment with local heat and analgetics was without effect. A roentgen examination six days later on 29 April showed a wedge-shaped compression fracture of the body of the sixth cer-

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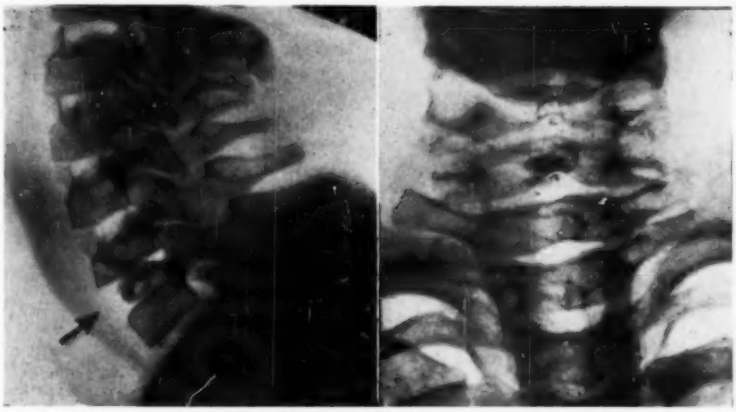


a. b.

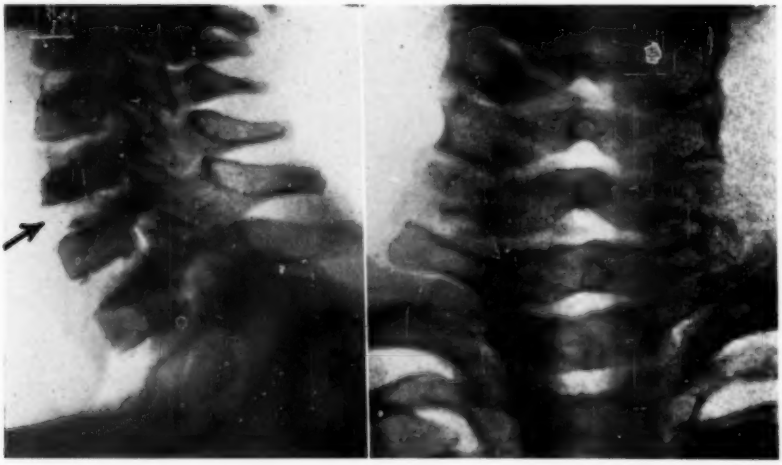
Fig. 1 a & b. April 29, 1952. Compressed body of C 6. Central calcification of nucleus pulposus below the compressed vertebra.

vical vertebra. There was marked calcification of the nucleus pulposus of the intervertebral disc between C 6 and C 7 (Figs. 1a and b). The remainder of the cervical and thoracic spine was normal. The patient had received no Vitamin D medication during the previous few years.

The fracture was treated by immobilizing the neck in a Thomas' collar. During the two weeks after the accident the pain subsided completely and the torticollis disappeared, a roentgen examination on 7 May showing almost complete disappearance of the calcification in the disc. The body of C 6 had increased in density (Figs. 2a and 2b). A few days later the collar was removed and no limitation of movement of the head and neck was found. More than a month later, on 12 June, roentgenograms still showed increased density of the body of C 6, but the intervertebral disc was completely free from calcification. Over a year later, in July 1953, the vertebral body was no longer increased in density, but still showed signs of compression. There was never any pain after the first two weeks following the accident.

Discussion

The clinical features of this case are to a large extent the same as the other six cases in the literature and discussed by WEENS (20). In all these reported cases, and in the present case, the lesions were situated in the cervical or upper thoracic spine. There was pain localized to the site of the lesion, and torticollis and/or limitation of movement were present. The calcification was confined to the centre of the disc. Clinical signs lasted only a few weeks, and the calcification disappeared in a short period of time. The calcification was post-traumatic in three of these cases, and presumed to be inflammatory in the others. The findings in the individual cases are listed in Table 1.



a. b.

Fig. 2 a & b. May 7, 1952. Calcification below the compressed vertebra, almost invisible; increased density of body of C 6.

This picture is quite different from the irreversible calcification of the peripheral parts of the disc found in the lower parts of the spine in adults. In such cases the lesions are usually asymptomatic and are found only incidentally when the patient is examined roentgenologically for other reasons.

It is possible that the variations in vascularization of the discs in childhood and in adult life may account in part for these differences.

Table 1

No.	Author	Age in years	Pain	History of trauma	Situation (all central)	Calcification first visible	Disappearance of calcification
1	Baron (2)	12	+	—	D 12—L 1	18 days	12 months
2	Kohlman (11)	12	+	+	D 4—D 5	"several days"	2 months
3	Lyon (13)'.....	8	+	+	C 6—C 7	21 days	5—8 months
4	Von Held (19)....	10	+	—	C 2—C 3 C 3—C 4 C 5—C 6	14 days	2 months
5	Keyzer (9)	2.5	+	—	C 2—C 3 C 3—C 4 C 4—C 5	30 days	"several months"
6	Weens (20)	5	+	—	C 6—C 7	"several months"	4 months
7	Present case	8	+	+	C 6—C 7	6 days	15 days

Fig. 3. June 12, 1952. Body of C 6 is markedly dense. The disc completely free from calcification.

Fig. 4. Examination, July 1953.

It is well known that up to the age of ten or occasionally even the age of 20 (8), there is a profuse blood supply to the intervertebral disc through numerous vascular channels which are embedded in and perforate the cartilagineous plates. These vessels originate in the spongiosa of the vertebral bodies and according to UEBERMUTH, are obliterated by fibrous changes and cartilagineous invasion in adolescence (18). BOEMIG (4) and CAMERA (7) verified these observations but found some of the vessels persisting after adolescence.

It appears to the writers that trauma to the highly vascularized disc in childhood may result in hemorrhage and hematoma formation, and subsequent calcification. The rich blood supply would probably predispose to rapid clearing of the calcification. In the four cases in the literature in which trauma is not known to have occurred, a rheumatic or other inflammatory origin is assumed. However, the possibility of mild trauma passing unnoticed in children cannot be excluded; even in the four cases quoted above the assumed inflammatory etiology is not entirely convincing.

In adults it is probable that the trauma of wear and tear plays a

major rôle in the calcification of the intervertebral disc, particularly in the lower part of the spine, the site of the greatest weight-bearing strain. Such trauma would be unceasing, and the predisposition to calcification continuous. The poor vascularization of the disc in older individuals would tend to inhibit clearing of the calcification. These factors together may cause permanence of the calcification.

The problem of mineral deposits in soft tissues is on the whole rather complicated. However, there is no doubt that as in a Pellegrini-Stieda's condition (10, 15), injury is an important etiologic factor. Even in calcified bursitis, trauma may be a causal factor (1, 5).

In our case, trauma was almost certainly the cause of calcification of the disc, although we have no roentgenologic evidence of absence of the lesion before the accident. The rapid clearing of the calcified deposits after the trauma makes it unlikely that the calcification was an incidental finding, and was present before the injury. Along with the other cases of intervertebral disc calcification in childhood, we consider that this case brings evidence to support the view that trauma is an important cause of calcification of a disc. The greater vascularity of the disc in childhood accounts for the rapid development and disappearance of the lesion. The marked density of the compressed vertebral body, interpreted as a vascular necrosis, likewise sustains our assumption that the vascular factor plays a major rôle in this condition.

Conclusions

1. Calcification of the intervertebral disc (i. v. d.) shows distinct differences in children and adults and may be described as two different entities.

2. In children the condition is rare.

(a) It is manifest by the clinical signs, severe transitory localised pain, deformity and limitation of movement of the head and neck.

(b) The calcified deposits are reversible.

(c) It is found in an i. v. d. of the cervical and upper thoracic spine.

(d) It is situated in the centre of the i. v. d., *i. e.* nucleus pulposus.

(e) It is of acute traumatic etiology, and may be a manifestation of a calcified hematoma.

3. In the older age groups the condition is rather frequent and in almost all instances

(a) without clinical signs

(b) mostly irreversible

(c) found in an i. v. d. of the lumbar and lower thoracic spine

(d) situated mostly in the peripheral part of the i. v. d., *i. e.* annulus fibrosus

(e) is of so-called degenerative origin (chronic trauma of wear and tear).

SUMMARY

A case is reported of an eight-year-old boy in whom calcification of a nucleus pulposus in the cervical region of C 6 was discovered roentgenologically six days after injury. The calcified deposits diminished in size and almost entirely disappeared some 10 days later. The significance of the vascularization as a predisposing factor in cases of calcified i. v. d. in childhood is discussed.

ZUSAMMENFASSUNG

Bei einem 8 Jahre alten Knaben wurde sechs Tage nach einem Trauma eine Verkalkung des Nucleus pulposus in der Gegend des 6. Halswirbels röntgenologisch entdeckt. Die verkalkten Ablagerungen nahmen an Grösse ab und verschwanden etwa 10 Tage später nahezu völlig. Die Bedeutung der Gefässversorgung als ein prädisponierender Faktor in Fällen mit verkalktem Discus intervertebralis in der Kindheit wird diskutiert.

RÉSUMÉ

Les auteurs présentent l'observation d'un garçon de huit ans chez qui l'examen radiographique a mis en évidence, six jours après un traumatisme, une calcification du nucléus pulposus dans la région cervicale, au niveau de C 6. Le dépôt calcaire a diminué de volume et presque entièrement disparu quelque dix jours plus tard. Les auteurs examinent l'importance de la vascularisation comme facteur prédisposant dans les cas de calcifications des disques intervertébraux chez l'enfant.

REFERENCES

1. Adler, E., and Maybaum, S.: A new clinical sign (Fall-Phenomenon) in bursopathia calcarea. Acta med. orient. 12 (1953), 261.
2. Baron, A.: Über eine neue Erkrankung der Wirbelsäule. Jahrb. f. Kinderh. 104 (1924), 357.
3. Barsony, T., and Koppenstein, E.: Calcinosis intervertebralis. Fortschr. Röntgenstr. 41 (1930), 211.
4. Boemig, R.: Die Blutgefässversorgung der Wirbelbandscheiben, das Verhalten des intervertebralen Chordasegments und die Bedeutung beider für die Bandscheibendegeneration. Arch. f. klin. Chir. 158 (1930), 374.
5. Cadman, E. A.: The Shoulder. Published by the Author, Boston 1934.
6. Calvé, J., and Galland, M.: Sur affection particulière de la colonne vertébrale simulant le Mal de Pott (calcification du nucleus pulposus). J. de radiol. et d'électrol. 6 (1922), 21.
7. Camera, U.: Escursioni attraverso patologia del disco intervertebrale. Boll. e mem. Soc. piemontese di Chir. 4 (1934), 142.
8. Coventry, M. B., Ghormley, R. K., and Kernshan, J. W.: The Intervertebral Disc: Part II, Changes in the Intervertebral Disc Concomitant with Age. J. Bone and Joint Surg. 27 (1945), 233.
9. Keyser: Cited by Weens.

10. KOHLER, A.: Roentgenology. English translation by Turnbulli, A., Baillere, Tindall and Cox, 2d. ed. pp. 188, London 1935.
11. KOHLMANN, G.: Cited by WEENS.
12. LANGE, E.: Schmerzen und Leistungsstörungen bei Erkrankungen der Wirbelsäule. Ed. Ferdinand Enke, Stuttgart 1937.
13. LYON, E.: Kalkablagerungen in der Zwischenwirbelscheibe in Kindesalter. Ztschr. f. Kinderh. 53 (1932), 570.
14. RATHCKE, L.: Über Kalkablagerungen in den Zwischenwirbelscheiben. Fortschr. Röntgenstr. 46 (1932), 66.
15. RUSSEL, D. A., and SMITH, C. D.: Pellegrini-Stieda Disease. Radiology 46 (1946), 351.
16. SANDSTRÖM, G.: Calcification of the Intervertebral Discs and the Relationships between Various Types of Calcification in the Soft Tissues of the Body. Acta radiol. 36 (1951), 217.
17. SCHMORL, G.: Verkalkungen der Bandscheiben der Wirbelsäule nebst Bemerkungen über das Verhalten bei inf. Spondylitis. Fortschr. Röntgenstr. 40 (1929), 18.
18. UEBERMUTH, H.: Die Bedeutung der Alterveränderungen der Menschlichen Bandscheiben für die Pathologie der Wirbelsäule. Arch. f. klin. Chir. 156 (1929), 567.
19. VON HELD, H. J.: Zwischenwirbelscheibenverkalkung. Dtsch. Z. f. Chir. 242 (1934), 675.
20. WEENS, H. S.: Calcification of the Intervertebral Discs in Childhood. J. Pediat. 26 (1945), 178.

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PYELOGRAPHY AFTER DIRECT PUNCTURE OF THE RENAL PELVIS

by

Ingmar Wickbom

The renal pelves are as a rule best and easiest examined by means of intravenous urography. This can, however, be done only provided the renal function is not too much impaired. If the function is altered to such a degree that no, or only incomplete filling of the renal pelves is obtained, other methods have to be used. If the unsatisfactory filling is caused by a highly vascular tumour this may be demonstrated by aortography. Aortography also gives information regarding the parenchyma and the renal vascularization. A hydronephrotic kidney has only a few narrow vessels and the cortical layer is thin. The same appearance may, however, also be seen in cases of poorly vascularized tumours such as sarcomas and carcinomas.

For the examination of the renal pelvis and the ureter in such cases retrograde pyelography has been used. This is, however, a fairly complicated procedure — especially in males — and cannot be employed if there is complete obstruction of the ureter. In a few of such cases the author has used a method of injecting the contrast directly into the pelvis after percutaneous puncture. The procedure having been found useful, a brief description of it may be of interest; as far as is known, it has not been used in other hospitals nor described in the literature.

Technique: The puncture is performed in roughly the same manner as in expanding lesions of the kidney. With the patient prone, two metal rods with small metal balls at 1 cm distance are placed at right angles

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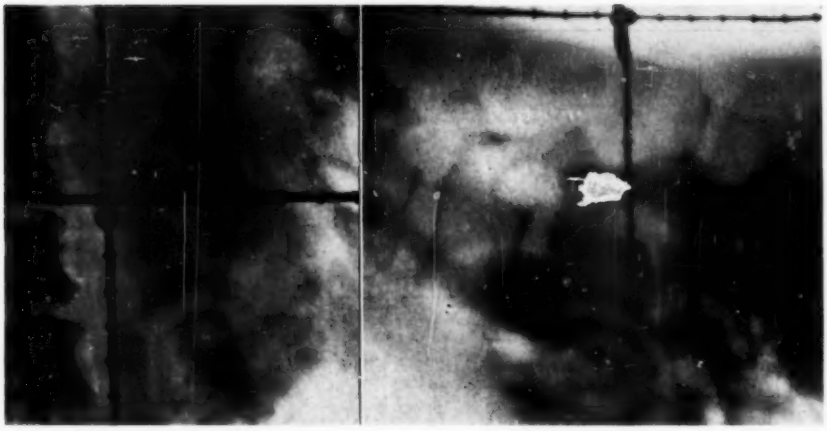

Fig. 1. Two metal rods with a cm scale are placed at right angles to each other on the skin of the back. A further rod is placed at the same level on the flank.

to each other on the skin of the back. The crossing-point should lie approximately over the renal pelvis. A similar rod is placed at the same level on the flank (Fig. 1). P. a. and lateral films are then obtained. From the co-ordinate system produced the best point for the puncture and the depth at which the pelvis should be found may be estimated. A long thin needle is used for the puncture.

So far, we have used the method in five cases only. In all of these there was hydronephrosis of moderate degree and no visible excretion on urography. This was caused in one case by a calculus and in the others by a tumour. In all the cases aortography failed to give a definite diagnosis. In none of them did the puncture cause any discomfort or other symptoms to the patient. At operation nothing was found that could be attributed to the puncture apart from small haemorrhages in the adipose tissue around the kidney in one case in which the kidney was removed two days after the puncture. Judging from these cases the method seems to be harmless.

At present we use the procedure only in cases in which the renal function is completely or almost completely abolished and in which no definite diagnosis can be obtained by aortography. It may be, however, that the method should be substituted generally for retrograde pyelography as well as in cases in which renal tuberculosis is suspected and intravenous urography gives only unsatisfactory results (for instance, due to impaired function). The risks of spreading urogenital tuberculosis

could possibly be diminished in this way. In two cases a slight leakage of the contrast medium could be seen at the site of the puncture.

In order to illustrate the method five cases will be briefly reported.

Case 1: M. J., male, aged 56. In May, 1947 a carcinoma of the transverse colon was removed. The patient was free from symptoms until June, 1952, when back pain started and haematuria was observed several times. On urography no excretion from the left kidney could be seen and aortography was therefore performed. The arteries to the left kidney were narrow and the cortical layer thin. No tumour vessels could be seen. To decide whether the changes were due to a tumour in the kidney or to an occlusion of the ureter the renal pelvis was punctured and 10 ml of Umbradil 35 % injected (Fig. 4). At operation (Prof. WESTERBORN) a tumour was found invading the ureter at the pelvic inlet and embracing the iliac artery. An attempt to remove the tumour had to be abandoned as it proved impossible to do this without ligating the iliac artery; furthermore, there were secondary deposits in the mesenterium.

Fig. 2. Case 1. Pyelogram after direct puncture of the left renal pelvis. The pelvis and the upper part of the ureter are dilated. There is a complete obstruction of the ureter at the pelvic inlet (arrow).

Case 2: A case of renal carcinoma. On urography no excretion from the left kidney was seen. Aortography showed the arteries to the left kidney to be narrow and the cortical layer very thin. Retrograde pyelography was performed but the pelvis could not be filled because of complete obstruction in the ureter (Fig. 3). When puncturing the pelvis in this case, only blood clots were encountered, a sign that the pelvis was filled by a tumour which was causing the obstruction in the ureter.

Case 3: A. B., female, aged 31. Five years before admission a left renal calculus was diagnosed. Since that time the patient had several typical attacks of pain in the back on the left side. On urography no excretion from the left kidney could be observed. There was a calcification the size of a hazel-nut at the site of the left renal hilum and several smaller ones in the lower part of the kidney. Aortography showed the cortical layer of the left kidney to be somewhat thin. The left renal pelvis was punctured and 10 ml of Umbradil 35 % injected. In the moderately dilated pelvis there were, apart from the obvious calculus, several well-defined filling defects (Fig. 4). These were supposed to be caused either by non-opaque calculi or by blood clots. At operation, however, no blood clots and only the calculi previously diagnosed were found. There was, however, a marked bulging of the renal columns into the pelvis corresponding to the filling defects seen in the pyelogram. In order to estimate whether this bulging alone could explain the filling defects, the pelvis of the specimen was filled with contrast medium. The pelvis having been opened immediately after the operation some leakage

Fig. 3. Case 2. Retrograde pyelography. Complete obstruction of the ureter.

Fig. 4. Case 3. Pyelogram after direct puncture of the left renal pelvis. Hydronephrosis of moderate degree. Calculi at the hilum and in the lower calyces. The filling defects are caused by a bulging of the renal columns into the pelvis.

unfortunately could not be avoided, but it was evident that the filling defects seen in the preoperative pyelogram were caused only by bulging of the renal tissue.

Case 4: J. B., female, aged 63. In 1924, luetic infection. The patient was admitted to the hospital for frequent and painful micturition during the previous weeks. Three days before admission blood clots were observed in the urine. On examination a large pulsating swelling was palpated at the site of the left kidney. On urography a rounded soft tissue mass was seen which could not be distinguished from the lower pole of the left kidney. No excretion was seen on that side. There were small calcifications in the periphery of the mass. Aortography showed an aneurysm of the aorta but this was much smaller than the soft tissue mass. The left renal artery was narrow and displaced upwards around the upper part of the tumour. The cortex of the left kidney was thin but could be seen also around the lower pole (Fig. 5). The left renal pelvis was punctured and some 10 ml of Umbradil 35 % injected. The pelvis was dilated but not deformed. The ureter, however, was displaced upwards in an arch around the upper part of the tumour which compressed it (Fig. 6). At operation (WESTERBORN) the tumour was found to be intimately connected to the aneurysm and could not be removed. Unfortunately no biopsy was performed.

Case 5: A. S., female, aged 69. The patient had observed passage of blood for a month and complained of frequent and painful micturition. On urography (Fig. 8)

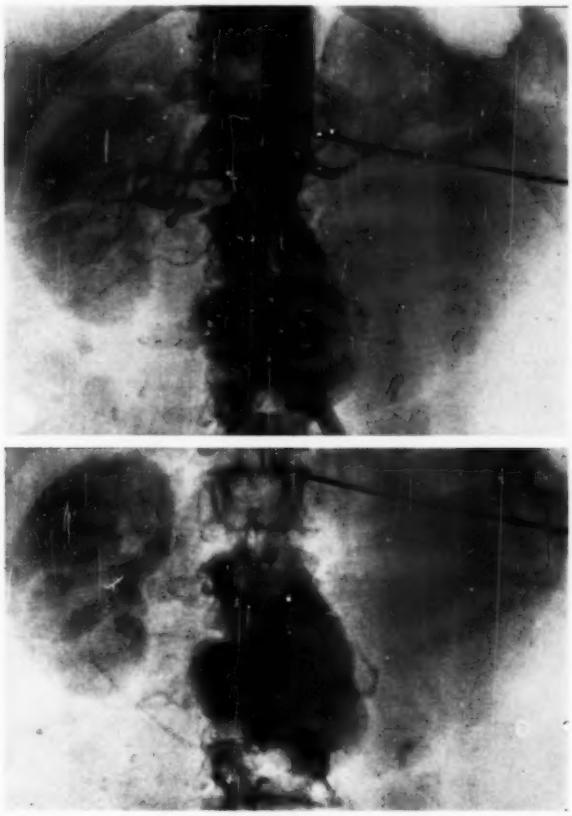

Fig. 5. Case 4. Aortography. *Top:* Arterial phase. Aneurysm of the aorta which does not, however, correspond with the whole of the soft tissue mass below the left kidney. The left renal artery is displaced upwards around this mass. *Below:* Two seconds later. The left kidney has only a thin cortical layer seen also around the lower pole showing that the soft tissue mass does not belong to the kidney.

a tangerine-sized tumour was seen in the lower pole of the right kidney. The renal pelvis was, however, not deformed. The upper pole of the kidney was broad and the distance between it and the uppermost calyx was increased. The left kidney was of normal size and shape, but no excretion could be seen from that side. The tumour at the lower pole of the right kidney was punctured and found to be a cyst. As there was no excretion from the left kidney and the haematuria could hardly be ascribed to the cyst in the right kidney, aortography was performed (Fig. 7). In the films, a cyst was seen also in the upper pole of the right kidney. The left renal artery and kidney appeared normal apart from a somewhat thin cortical layer. The renal pelvis on the left

Fig. 6. Case 4. Pyelography after direct puncture of the pelvis. Hydronephrosis of moderate degree. The ureter is displaced upwards and compressed by the tumour.

Fig. 7. Case 5. Aortography. *Top:* Arterial phase. Two renal arteries on the right side and three on the left. *Below:* Three seconds later. Cyst in the upper as well as the lower pole of the right kidney. The left kidney appears normal.

Fig. 7.

side was punctured and 10 ml of Umbradil 35 % injected. The pelvis was moderately dilated as was the ureter down to the bladder where almost complete obstruction was present (Fig. 9). Cystoscopy because of extensive bleeding failed to give any information. On cystography, however, a tumour was seen in the posterior wall of the bladder, invading the orifice of the left ureter. This was confirmed at operation.

SUMMARY

A method is described for examination of the renal pelvis after percutaneous puncture and injection of a contrast medium directly into the pelvis. The method is used

Fig. 8. Case 5. Urography. The lower as well as the upper pole of the right kidney are enlarged but the pelvis is not significantly deformed. (There was no contrast filling of the pelvis on the left side.)

Fig. 9. Pyelography after direct puncture of the left pelvis. The pelvis and the ureter down to the bladder are slightly dilated.

mainly in cases in which no excretion is seen from one kidney during urography and in which the appearances on aortography are compatible with hydronephrosis or an avascular tumour. Five illustrative cases are briefly reported.

ZUSAMMENFASSUNG

Eine Methode zur Untersuchung des Nierenbeckens nach perkutaner Punktion und Injektion eines Kontrastmittels direkt in das Becken wird beschrieben. Die Methode ist hauptsächlich in solchen Fällen benutzt worden, bei denen man bei der Urographie keine Kontrastausscheidung sah und bei denen das Aussehen bei der Aortographie mit einer Hydronephrose oder einem gefässarmen Tumor stimmen kann. Fünf illustrative Fälle werden kurz berichtet.

RÉSUMÉ

Description d'une méthode d'examen du bassinet rénal par ponction percutanée et injection de produit de contraste directement dans le bassinet. Cette méthode est utilisée surtout dans les cas où un rein ne donne pas par urographie d'excrétion visible et où les images aortographiques sont compatibles avec les diagnostics d'hydronéphrose ou de tumeur avasculaire. Présentation de cinq cas.

REFERENCES

Fish, G. W.: Large solitary serous cysts of the kidney. J. A. M. A. 12 (1939), 514.

Lindblom, K.: Percutaneous puncture of renal cysts and tumours. Acta radiol. 27 (1946), 66.

Wheeler: Use of the aspirating needle in the diagnosis of solitary renal cyst. New England J. Med. 226 (1942), 55.

FROM THE ROENTGENDIAGNOSTIC DEPARTMENT II (DIRECTOR: W. MAGNUSSON), SÖDERSJUKHUSET, STOCKHOLM, SWEDEN

ON THE LOCALIZATION OF TUBAL OBSTRUCTION IN CASES OF STERILITY FROM DIFFERENT CAUSES

by

Wolfgang Magnusson

In the rather abundant earlier literature on hysterosalpingography (HSG) in cases of sterility, the opinion has been generally expressed, that tubal obstruction can be readily localized but that the examination cannot give any information as to the nature of the pathologic process causing the obstruction (6, 2, 3).

Later, however, it has been shown that in tubal endometriosis (5), and tubal tuberculosis (4), typical roentgen-anatomic signs often make the diagnosis of the nature of these processes possible. In tubal obstruction caused by other conditions of an inflammatory nature in the tubes or pelvic peritoneum, no specific signs related to the origin or nature of the inflammation have been described. It has been stressed, however, that HSG as a rule is first performed after the infection has healed, and that the visible remnants after different infections have the same HSG appearances. Reliable facts, however, have not been presented as a basis for this conception. Nor, as far as the author is aware, has any attempt been made to examine the situation of tubal obstructions in relation to information concerning the causes, gathered from case histories.

A priori, it would seem unlikely, that inflammation following delivery or abortion should cause obstruction at the same site as inflammation spreading from the peritoneal cavity and in which the tube is secondarily affected. In the former case the obstruction should more often be situated in the neighbourhood of the uterine end of the tube and in the latter case in the fimbriated end.

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A critical examination of the histories in cases with different sites of tubal obstruction would, therefore, appear to be of value. In this connection one must, however, bear in mind that the case histories are often unreliable for the assessment of the causes of sterility. Many patients, for example, deny having had gonorrhoea or an abortion, when such causes of sterility have existed.

Another rather important difficulty in the assessment lies in the fact that the histories often contain information about many possible causes of sterility, for example, abortion, gonorrhoea, and appendicitis in the same case.

All these sources of error should involve a lower frequency of gonorrhoea and abortion in the histories than really exist, but they probably have the same effect on both groups, irrespective of the situation of the obstruction.

Another fact of importance in this connection is that bilateral obstructions in the uterine ends of the tubes, diagnosed by HSG, do not preclude the possibility of obstructions at the fimbriated ends also being present. The frequency of such closures of both ends on the same side cannot be estimated from our material. Observations at operations seem to indicate that this is a rather rare occurrence. HOLTZ (1) in a paper concerning the operative technique in the treatment of female sterility, describes his experiences in the following way: "Lors d'occlusion à la jonction utérotubaire, il semble que très souvent la cause ait été un avortement fébrile suivi d'endométrite. Les trompes au delà de l'obstacle ainsi que les ovaires sont sains. C'est pourquoi l'implantation tubo-utérine donne des résultats très supérieurs à la salpingostomie."

In our material of female sterility we have 55 cases (Group 1), in which bilateral obstruction in the uterine ends of the tubes was found on HSG and 134 cases with bilateral obstruction in the fimbriated ends (Group 2). Cases in which a specific cause such as endometriosis or tuberculosis has been given have been excluded.

In Group 1 the frequency of secondary sterility was 56.4 % (thirty-one cases, of which fifteen were abortions and four were extrauterine pregnancy). In Group 2 the same frequency was 24.6 % (thirty-three cases, of which fourteen were abortions). The difference in the frequency of secondary sterility in the two groups was thus 31.8 ± 7.65 % and in the frequency of abortions, 16.7 ± 6.5 %.

The figures indicate that in bilateral obstructions at the uterine ends of the tubes complications from the puerperium and abortion are a more frequent cause of the blocks than in bilateral obstructions at the fimbriated ends. Such complications, however, may give rise to obstructions at both extremities of the tubes. The results are thus well in accord with the experiences of HOLTZ (1).

Salpingitis following, but without obvious connection with, pregnancy or abortion, has been noted in one case in Group 1, and in thirteen cases in Group 2. It is therefore most probable that the difference in the real frequency of complications with pregnancy and abortion as the cause of obstruction, is higher than the figures indicate.

The case histories contain information about gonorrhoea in two cases in Group 1. In one of these the patient later on had an abortion. In this case the gonococcal infection obviously cannot have caused the obstruction, at least, not on both sides. In Group 2 there was a history of gonorrhoea in eight cases. In seven of these it was a question of primary sterility. In the remaining case gonococcal salpingitis had occurred after pregnancy. The figures are too low for valid conclusions, but seem to indicate that the gonococcal infection seldom gives rise to obstruction at the uterine ends of the tubes.

The histories also contain information about peritonitis associated with appendicitis in two cases in Group 1, both with primary sterility. In one of these the patient later developed salpingitis without any obvious connection with the appendicitis. In Group 2 the same information was given in seven cases. These figures are also too low for valid conclusions but indicate that appendicitis is a more infrequent cause of sterility, and that the obstructions in such cases are most often situated in the fimbriated ends of the tubes.

Finally, it may be noted that bilateral obstruction at the uterine openings may occur both in tuberculosis and endometriosis, as well as with tumours. The diagnosis from HSG is in such cases dependent upon the uterine changes and will not be dealt with in this paper.

SUMMARY

In a hysterosalpingographic material of 189 cases, attention was directed to the situation of tubal obstruction in cases of sterility from different causes. Complications of the puerperium and of abortion were the most frequent cause of both tubes being blocked at the uterine ends. Gonorrhoea was seldom followed by such obstruction. Peritonitis associated with appendicitis more frequently caused obstruction in the fimbriated ends.

ZUSAMMENFASSUNG

In einem hysterosalpingographischen Material von 189 Fällen wurde der Lage des Tubenverschlusses bei Sterilitäten verschiedener Ätiologie besondere Aufmerksamkeit gewidmet. Komplikationen im Puerperium und bei Aborten waren die häufigste Veranlassung zur Blockade der uterinen Enden beider Tuben. Gonorrhoë verursachte eine derartige Obstruktion selten. Eine Peritonitis, die im Anschluss an eine Appendicitis auftritt, verursacht häufiger eine Obstruktion der Ampullen.

RÉSUMÉ

Sur un matériel de 189 cas d'hystérosalpingographie, l'auteur s'est attaché à préciser le siège de l'obstruction tubaire dans des cas de stérilité de diverses causes. Les complications de l'accouchement et de l'avortement se sont montrées la cause la plus fréquente d'obstruction des deux trompes à leur extrémité utérine. La blennorragie a rarement été suivie d'obstruction de ce type. La péritonite appendiculaire a causé le plus souvent une obstruction des ampoules.

REFERENCES

1. Holtz, F.: Techniques opératoires dans le traitement de la stérilité féminine. Conférences du Congrès international jubilaire de la Société Française de Gynécologie. Paris 1951.
2. Kjellberg, S. R.: Hystero-salpingo-pelvigraphie. Acta radiol. Suppl. XLIII (1942).
3. Madsen, V.: Kliniske Studier over Hysterosalpingografi (Danish). Universitetsforlaget, Aarhus, Denmark 1942.
4. Magnusson, W.: Über das Röntgenbild bei tuberkulöser Salpingitis. Acta radiol. 26 (1945), 265.
   — Further experiences in the roentgen diagnosis of tuberculous salpingitis. Acta radiol. 28 (1947), 824.
5. Philipp, E., and Huber, V.: Vergleichende histologische und röntgenologische Untersuchungen über den interstitiellen Tubenabschnitt. Fortschr. Röntgenstr. 60 (1939), 1.
6. Schultze, G. K. F.: Gynäkol. Röntgendiagnostik. Ferdinand Enke Verlag, Stuttgart, Germany 1939.

FROM THE RADIUM CENTRE (DIRECTOR: JENS NIELSEN), COPENHAGEN, DENMARK

DYSPHAGIA IN BULBAR AND PSEUDOBULBAR LESIONS SIMULATING OESOPHAGEAL CARCINOMA

by

Erik Madsen

Among 108 patients with benign lesions referred to the Radium Centre, Copenhagen, during the period 1940—1950 suspected of oesophageal carcinoma, 7 had bulbar or pseudobulbar lesions.

These seven cases will be reported partly in order to discuss the differential diagnosis from oesophageal carcinoma and partly to show that certain findings ought to suggest bulbar lesions even in the absence of definitely pathognomonic roentgen signs.

The involuntary part of the act of swallowing begins when the food has reached the oropharynx. At that stage certain reflexes are elicited, mainly by way of the glossopharyngeal and superior laryngeal nerves. These reflexes shut off the nasopharyngeal isthmus and the aditus laryngis. Respiration is arrested by a reflex excited through the glossopharyngeal nerve. The oesophageal muscles begin to function. The regulation of the peristaltic movement in the oesophagus is controlled by impulses from the central nervous system to each segment through the respective nerve branches. The motor fibres of the glossopharyngeal and vagus nerves originate in part in the dorsal vagoglossopharyngeal nucleus and in part in the nucleus ambiguus.

Dysphagia is a sign of various lesions in the medulla oblongata; it is thus a link in the syndrome of bulbar palsy which in addition includes dysarthria and respiratory embarrassment. There will be paresis of the soft palate, in some cases also involving the pharynx and vocal cords — as well as atrophy and paresis of the tongue.

Dysphagia may, moreover, be a result of injury to the supranuclear cortical innervation, usually due to cerebral arteriosclerosis.

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These bulbar conditions may be caused by progressive bulbar palsy, *i. e.* an amyotrophic lateral sclerosis of bulbar situation (one case) or thrombosis in the inferior posterior cerebellar artery giving rise to an infarct in the medulla oblongata — the so-called Wallenberg syndrome — (three cases). Moreover, there may be a question of encephalitis, poliomyelitis, tumours, and traumatic lesions. The present series also includes a case in which the diagnosis was probably pontobulbar thrombosis. In pseudobulbar palsy, dysphagia is usually caused by pronounced cerebral arteriosclerosis (two cases).

Case Reports

Case I. A female, aged 64, who had on the whole been in good health. For the last 6 months atypical attacks of dizziness. During the previous month increasing blurring of speech and a tendency for food to pass into the larynx. Owing to these symptoms the patient was referred to the Radium Centre for suspected oesophageal carcinoma without previous roentgen examination.

Physical examination: Small, lean woman. Speech of bulbar type, almost incomprehensible. Paresis and atrophy of the lips. The tongue, which showed atrophic marginal notches, was the seat of fibrillations and could be extended only weakly. Laryngoscopy revealed paresis of the left piriform fossa. No neurologic abnormalities in the extremities.

Roentgen examination of the oesophagus and stomach showed no abnormality.

There was hardly any doubt that in this case the correct diagnosis was progressive bulbar palsy.

Case II. A male, aged 73, previously in good health. During the last three months a tendency for food to pass into the larynx. No disturbances of speech. Apt to cry, but no other psychic affection. The patient was referred to us because of dysphagia, without previous examination of the oesophagus.

Physical examination: Fair general condition. Mentally marked by greatly impaired hearing, but did not appear demented. Apparently no disturbances of speech. Laryngoscopy showed paralysis of both thyro-arytenoid muscles, but no other abnormality. Neurologic examination revealed no abnormality apart from somewhat suspicious plantar reflexes. Poor pulsation in the arteries of the feet.

Roentgen examination of the oesophagus showed passage of considerable amount of contrast medium into the larynx and trachea, but no other abnormality. Normal appearances of the stomach.

Oesophagoscopy: No abnormality.

The condition was most probably one of pseudobulbar paralysis, due to cerebral arteriosclerosis.

Case III. A male, aged 81, previously in good health. For the last 6 months increasing dysphagia, the food passing into the larynx, and at the same time increasing blurring of speech. Referred to the Radium Centre, as a roentgen examination of the oesophagus suggested cancer.

Physical examination: Extremely senile. Speech of bulbar type, almost incomprehensible. Neurologic examination revealed no other abnormalities.

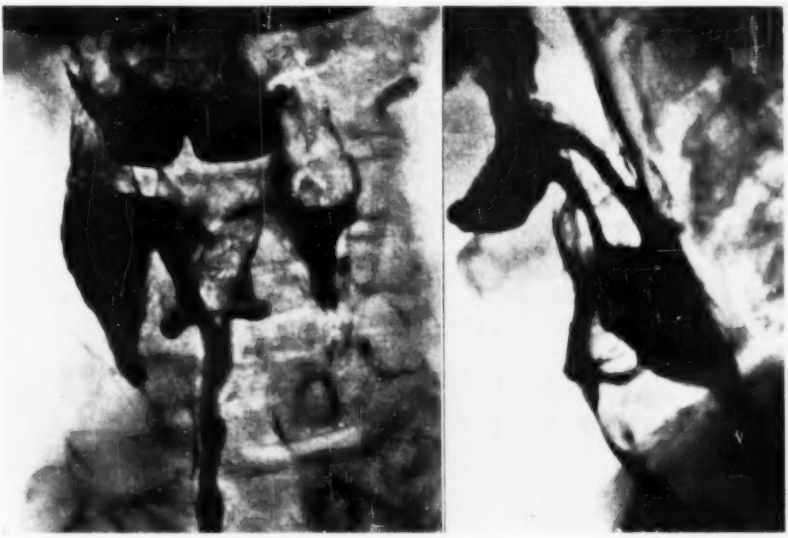

Fig. 1. Accumulation of barium in the pharynx and passage of the bolus into the trachea and larynx.

On roentgen examination the opaque medium was seen to accumulate in the hypopharynx, some of it passing into the larynx and trachea; slow passage through the oesophagus, but no signs of tumour. Pronounced arteriosclerosis of the arch of the aorta.

The diagnosis was somewhat uncertain, but the condition was most likely to have been pseudobulbar palsy due to cerebral arteriosclerosis.

Case IV. A male, aged 43, who had on the whole been in good health. The onset of the present illness had been insidious in the form of occipital headache one year previously. The condition remained fairly stationary for 6 months and then the headache disappeared. For the last 3 months hoarseness and dysphagia, a tendency for food to pass into the larynx, and regurgitation. At the same time occasionally diplopia, the patient seeing the objects beside each other, but this phenomenon gradually subsided. In addition, a sensation of numbness in the left side of the face and left arm and weakness of the left extremities, mainly the arm.

Fig. 2. Asymmetric accumulation of barium in the left hypopharynx.

As a roentgen examination gave rise to a suspicion of oesophageal carcinoma, the patient was admitted to the Radium Centre.

Physical examination: Fair to poor general condi-

tion. No ocular abnormality apart from left-sided corneal hypaesthesia. Left-sided paresis of the soft palate. Laryngoscopy showed paresis of the left side of the hypopharynx and larynx. Hoarse voice. Diffuse paresis of the left upper extremity, uncertainty in the finger-to-nose test, and deep areflexia. Right arm and both lower limbs normal. Abdominal reflexes diminished on the left. Hemihypaesthesia on the left side, reaching from forehead to groin.

Roentgen examination of the oesophagus showed asymmetric accumulation of the opaque medium in the left side of the hypopharynx and left piriform fossa. No signs of tumour (Fig. 2). Tomograms of the larynx disclosed paresis of the left vocal cord; the left piriform fossa was deep and broad.

Oesophagoscopy showed nothing abnormal.

The diagnosis was in some doubt. The possibilities of pontobulbar encephalitis and syringomyelia of a bulbar nature were considered, but the neurologist was most inclined towards pontobulbar thrombosis.

Case V. A female, aged 61, with diabetes mellitus of 6 years' standing treated with insulin. About 5 months previously the patient suddenly developed neuralgiform pain in the left side of the face. Dysphagia supervened and her voice became aphonic. The symptoms had remained unchanged, and the patient had lost about 20 kilos in weight. As the roentgen appearance gave reason to suspect a tumour in the upper part of the oesophagus and as the oesophagoscope could not be passed lower than the upper end of the oesophagus, the patient was admitted to the Radium Centre with suspected oesophageal carcinoma.

Physical examination: Good general condition. Voice aphonic. Left pupil somewhat larger than the right. Hyperaesthesia of the left side of the face, especially in the areas innervated by the first and second branches of the trigeminal nerve; uncertain thermal sense in the same areas. Paresis of the left side of the soft palate, pharynx, and vocal cords. Uncertain thermal sense in the right extremities.

Roentgen examination of the oesophagus showed slow passage of the barium down the oesophagus with retention in the valleculae and piriform fossae.

Diagnosis: Thrombosis of the posterior inferior cerebellar artery (Wallenberg).

Case VI. A male, aged 51, who had been in good health. Acute onset 6 months previously in the form of dysphagia and a feeling of cold and pain in the right side of the face. The patient was admitted to the Otologic Department of the Copenhagen County Hospital in Gentofte, where Wallenberg's syndrome was diagnosed. As the patient was practically unable to swallow, gastrostomy was performed one month later. Some time after, the patient was sent to a surgical department where oesophagoscopy was attempted, but given up as the oesophagoscope stopped short at the upper end of the oesophagus. The patient was now referred to the Radium Centre in the belief that he might be suffering from a carcinoma situated high up in the oesophagus (incidentally, an extremely uncommon site in males).

Physical examination: General condition good. Mentally normal. Laryngoscopy revealed incomplete right-sided laryngeal paresis with the vocal cord in abduction. Neurologic examination revealed an atypical plantar reflex on the left side but no other abnormality.

In the roentgen examination of the oesophagus, the patient had difficulty in swallowing the barium which tended to run into the larynx, but as soon as the bolus had entered the oesophagus the passage was normal and there were no signs of tumour.

From the history there was no doubt that the patient had had thrombosis of the posterior inferior cerebellar artery (Wallenberg).

Case VII. A male, aged 75. From 37 to 42 years of age he had been treated for lupus vulgaris, inter alia, with roentgen irradiation to the left side of the neck and the left cheek.

Six weeks prior to admission, the patient suddenly had severe hiccough, nausea, vomiting, pain in the throat on swallowing, and hoarseness. No symptoms in the arms or face. He was referred to the Radium Centre, because the roentgen appearances suggested oesophageal carcinoma.

Physical examination: Good general condition, perhaps somewhat senile. Depigmentation and cicatricial changes on the skin of the left cheek and neck following the previous radiotherapy. Laryngoscopy revealed paresis of the left half of the larynx with the vocal cord in adduction. Left piriform fossa flattened and infiltrated, presumably due to cicatricial shrinkage resulting from the radiotherapy. To be on the safe side, however, we removed a biopsy specimen which showed simple epithelial thickening. Neurologic examination revealed that the right pupil was larger than the left, but no other abnormalities.

Roentgen examination of the pharynx and oesophagus showed retention in the valleculae and piriform fossae. Spasm of the entire oesophagus, and delayed passage of the barium. When the examination was repeated the barium entered the larynx and trachea, but there was no spasm.

The acute onset with hiccough and nausea indicated a vascular lesion of the central nervous system, but in the absence of sensory disturbances in the face or cerebellar signs in the upper limbs, we could only make a tentative diagnosis of thrombosis of the posterior inferior cerebellar artery (atypical Wallenberg syndrome).

Discussion

In bulbar and pseudobulbar lesions like those reported above, dysphagia is a more or less pronounced sign which, however, seldom leads to reference of the patient to hospital for suspected oesophageal carcinoma.

Several Scandinavian workers, including WINTHER, ASTRUP, and STENSRUD have reported on Wallenberg's syndrome, but dysphagia was not an outstanding sign in any of their cases. The aetiology is occlusion of the posterior inferior cerebellar artery, but owing to anatomic variations the syndrome may also be due to lesions in other vessels.

Myasthenia gravis is sometimes discussed in relation to the pareses of swallowing. In this condition dysphagia is often extremely marked. VIETS found dysphagia and dysarthria to be the initial signs in 35 out of 175 cases.

In this connection it might be interesting to mention a case of dysphagia myogenica from the Radium Centre, published by BECH-MATHIESEN. The patient was a 72-year-old man referred to the Centre because a roentgen examination had suggested oesophageal carcinoma. The patient had been suffering from dysphagia for about 6 years, fairly constant during the first 5 years, but aggravated during the 9 months preceding admission. Roentgen examination showed slow passage of the barium down the upper part of the oesophagus and filling of both piri-

form fossae. Oesophagoscopy showed no abnormality. The patient exhibited diffuse muscular atrophy affecting the proximal muscles more than the distal ones. The neurologic conclusion was: Cryptogenetic, progressive myogenous muscular atrophy. Dysphagia was also a link in this syndrome. The condition is rare, but it is of differential diagnostic interest, as it may be mistaken for oesophageal carcinoma in a cachectic patient.

In cases of peripheral pareses of swallowing the disturbance in the swallowing reflex is due mostly to lesions of the superior laryngeal and glossopharyngeal nerves, where the centripetal, sensitive arch of the reflex is situated. As is well known, the cause may be various intoxications, infection, tumours, and trauma.

The roentgenologic signs in cases of bulbar and pseudobulbar lesions may be one or more of the following: passage of the barium into the larynx and trachea, its accumulation in the pharynx, retention of the contrast medium in the valleculae and piriform fossae, and its slow passage down the oesophagus. Passage of the barium into the larynx and trachea does not depend solely on the capacity of the larynx to close, but also on the pharyngeal muscles. In the presence of pharyngeal paresis, the contrast medium will accumulate in the pharynx and may remain there long enough to be spilled into the larynx and trachea by inspiration even in the absence of laryngeal paresis. Repeated passage of the bolus into the pharynx and trachea will gradually reduce the sensibility of the trachea and bronchi. This means that the cough reflex is not so easily excited and the patients will be apt to develop pneumonia.

At times, a roentgen examination of the oesophagus may fail to reveal any abnormality, even though there is a long history of the food passing into the larynx. The explanation is often that fluids are more prone to find their way into the larynx. This may be investigated by administering a more fluid opaque medium after the usual thick barium emulsion.

Retention of the opaque medium in the valleculae epiglotticae and piriform fossae is often termed "the vallecular sign". It consists of four symmetrical shadows, the upper two at the sites of the valleculae and the lower two corresponding to the piriform fossae. But not even this sign is pathognomonic of a swallowing paresis, as it may also occur in cases of cachexia or heart disease. In such instances, it may be explained by the reduced tonus of the oesophagus which accompanies these conditions.

In the normal process of swallowing, the food stream is divided at the epiglottis by the glosso-epiglottic fold, reaching the valleculae, where it is checked momentarily, whereupon it continues over the pharyngo-epiglottic folds into the lateral food channels in order to meet

at the upper end of the oesophagus. ARDEN & KEMP have described the roentgen appearances of normal swallowing.

The opaque medium may sometimes pass slowly down the oesophagus and be due to deficient peristalsis. In cases of greatly reduced tone of the oesophagus, however, the passage may be accelerated. A slow passage is more rarely due to spasm. The oesophagus may then appear as a narrow ribbon or show several circular areas of spasm, simulating a string of pearls. If the spasm is very pronounced, the appearances seen in the roentgen film will suggest that the barium could not force its way down the oesophagus. In that case, the condition may be difficult to distinguish from organic stenosis; the correct diagnosis may, however, usually be made upon further examination, as the spasm at certain times relaxes spontaneously. It may also be worth trying to relieve it by atropine although this is not always effective.

Atony and spasm are closely related, both reflecting disturbances of the vegetative nervous system.

SUMMARY

Seven patients with bulbar or pseudobulbar lesions were referred to the Radium Centre, Copenhagen, for suspected oesophageal carcinoma. Roentgen examination of the oesophagus revealed one or more of the following signs: Passage of the bolus into the trachea, accumulation of the opaque medium in the pharynx, its retention in the valleculae and piriform sinuses, and a delayed passage down the oesophagus.

ZUSAMMENFASSUNG

Sieben Patienten mit bulbären und pseudobulbären Läsionen sind unter dem Verdacht eines Ösophaguskarzinomes zum Radiumzentrum in Kopenhagen geschickt worden. Die Röntgenuntersuchungen ergaben eines oder mehrere der folgenden Symptome: Kontrastpassage in die Trachea, Anhäufung des Kontrastmittels im Pharynx, Retention des Kontrastes in den Valleculae und im Sinus piriformis sowie verzögerte Kontrastpassage im Ösophagus.

RÉSUMÉ

Sept malades atteints de troubles bulbaires ou pseudobulbaires ont été adressés au Centre du Radium de Copenhague comme suspects de cancer de l'oesophage. L'examen radiologique de l'oesophage a montré un ou plusieurs des signes suivants: Passage du bol alimentaire dans la trachée, accumulation du produit opaque dans le pharynx, rétention dans les vallécules et les sinus piriformes et retard de son passage dans l'oesophage.

REFERENCES

ARDRAN, G. M. and KEMP, F. H.: The mechanism of swallowing. Proc. Roy. Soc. Med. 44 (1951), 1038.

ARDRAN, G. M. and KEMP, F. H.: The protection of the laryngeal airway during swallowing. Brit. J. Radiol. 25 (1952), 406.

Astrup, E. Carsten: Wallenbergs syndrom (Norwegian). Nord. med. 40 (1948), 2156.
Bech-Mathiesen, H.: Ejendommelig dysphagi opfattet som cancer oesophagi (Norwegian). Nord. med. 44 (1950), 1761.
De Jong Russell, N.: The neurologic examination. Harper, New York 1950.
Stensrud, Per A.: Wallenbergs syndrom (Norwegian). Nord. med. 47 (1952), 1622.
Viets, H. R.: Diagnosis of myasthenia gravis in patients with dysphagia. J. A. M. A. 134 (1947), 987.
Winther, K.: Etude sur les syndromes hémi-bulbaires. I. Les voies sympatiques dans les bulbes. Acta psychiat. et neurol. 7 (1932), 719.

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A STUDY ON THE EFFECT OF S^{35}-LABELLED SODIUM SULPHATE ON FERTILITY IN MICE

by

Erik Odeblad and *Harry Boström*

In earlier papers (BOSTRÖM and ODEBLAD, 1952, ODEBLAD and BOSTRÖM, 1953) it was shown that S^{35}-labelled sulphate is accumulated in the ovaries of the rabbit and rat, especially in the granulosal cells and the follicular fluid. The egg cell did not accumulate much S^{35} (ODEBLAD, 1952). The same facts also hold for mice, as shown in fig. 1. Because S^{35} emits soft beta rays with a half range of about 40 μ and a maximum range of about 300 μ in tissue, it seemed possible to obtain a more or less selective irradiation of the follicular contents in the ovary. It was believed that this irradiation among other things might be reflected in decreased or completely inhibited fertility of animals injected with radioactive sulphate in appropriate dosage.

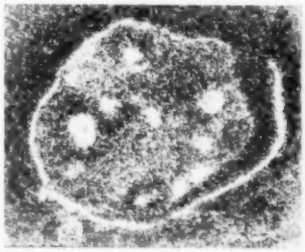

Fig. 1. Autoradiograph of an ovary of a mouse injected with S^{35}-labelled radiosulphate. The light areas correspond to heavy accumulation of radiosulphate. This is mainly situated in the follicles and the bursa ovarii. Magnification × 20.

Experimental

Because of their suitable size and short gestation period, mice were chosen as experimental animals. Three hundred and twenty-three adult female mice of the strain An 52 were used, three to six months old.

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They were subdivided in nine experimental groups as indicated in table I. The control group (C) was not treated with radioisotope, while the other experimental groups received amounts of S^{35}-labelled sulphate in carrier-free solution varying from 0.5 to 60 μC/g (microcuries per gram of body weight), as shown in table I.

Table I

I	II	III	IV	V	VI
C	—	55	20	36	8
1	0.5	34	10	29	7
2	2	21	5	24	8
3	3.8	31	13	42	8
4	5	19	3	16	—[1]
5	7.5	26	1	4	11
6	10	22	7	32	7
7	15	27	11	41	7
8	30	45	14	31	11
9	60	43	7	16	9
	Total —	323	91	28	—

Columns: I: Experimental groups.
II: Dosage of S^{35} in μC/g.
III: Number of female mice in the group.
IV: Number of pregnant animals in the group.
V: Percentage of pregnant animals.
VI: Mean number of embryos per pregnancy.

All the female mice were kept separated from the males at least four weeks before the injection of radiosulphate in order to secure that none was pregnant. One week after the injection of radiosulphate, the males were allowed to live together with the female mice. The proportion of males to females was about 1 : 2. The males were removed after one week, and after another week had passed, the female mice were killed, and the number of pregnant animals and number of embryos were recorded.

The ovaries and the uteri were also examined in situ and histologically.

Three of the animals in group 9 died some days before the final examination. None of them was pregnant.

Results

The results are shown in table I. The percentage of pregnant animals showed no regular relation to the dosage of S^{35}. The variations may be explained on a statistical basis and may also be due to variations in male and female fertility, impossible to control. The important finding

[1] Results missing.

is that the female fertility was not completely inhibited even at the very high dosage of 60 μC/g. It is also interesting to note that no morphologic damage could be seen with certainty in the ovarian follicles. The examination of the uteri of the non-pregnant animals showed the presence of various cyclic phases, indicating that no severe endocrine insufficiency of the ovaries occurred.

Discussion

The high dosage of radiosulphate allowing fertility in the female mice seems at first somewhat surprising. However, the excretion of radiosulphate during the period of the experiment was high (90—95 per cent), and the energy of the beta radiation low (about 0.16 MeV); both these facts contribute to reduce the effect of internal irradiation of radiosulphate when compared with *e. g.* radiophosphate (P^{32}) (ODEBLAD, 1952).

A dose of S^{35} producing inhibition of fertility will probably be found at still higher dosage levels than those used here. To find the dosage for this effect involves expensive experiments, and the information has no practical significance at present since no internal contamination nor diagnostic procedure with radiosulphate seems to require dosage levels in humans comparable with 60 μC/g in mice. Below this level no severe inhibition of fertility is indicated by this investigation. We have, however, examined only a limited time interval after the administration and too wide conclusions should not be drawn from our results.

SUMMARY

Groups of adult female mice were given amounts of S^{35} (sulphate) varying from 0.5 to 60 μC/g. The fertility in the various groups was tested by recording the percentage of pregnant animals and number of embryos per pregnancy. Even at the highest dosage levels studied, no complete inhibition of fertility occurred, and histologic damage of the ovaries was not observed with certainty.

ZUSAMMENFASSUNG

Gruppen junger weiblicher Mäuse wurde S^{35} in Mengen zwischen 0.5 und 60 μ C/g gegeben. Die Fertilität der verschiedenen Gruppen wurde durch Registrierung des prozentuellen Anteiles trächtiger Tiere und der Anzahl der Embryonen per Geburt geprüft. Auch bei den höchsten untersuchten Dosisgrenzen trat keine völlige Hemmung der Fertilität auf und eine histologische Schädigung der Ovarien konnte nicht mit Sicherheit beobachtet werden.

RÉSUMÉ

Des lots de souris femelles adultes ont reçu des quantités de S^{35} (sulfate) allant de 0.5 à 60 μ C/g. La fertilité des différents lots a été appréciée en notant le pourcentage d'animaux gravides et le nombre d'embryons par gravidité. Même les plus fortes doses étudiées n'ont pas entraîné une inhibition complète de la fertilité et on n'a pas observé de façon certaine de lésion histologique des ovaires.

REFERENCES

BOSTRÖM, H. and ODEBLAD, E.: Autoradiographic observations on the uptake of S^{35} in the genital organs of the female rat and rabbit after injection of labelled sodium sulphate. Acta endocrinol. 10 (1952), 89.

ODEBLAD, E.: A study of the short-time effects on the mouse ovary of internal irradiation with P^{32}. Acta radiol. 38 (1952), 33.

— Unfertilized rabbit ova in S^{35}-autoradiography. Exper. Cell Research 3 (1952), 694.

— and BOSTRÖM, H.: A time-picture relation study with autoradiography on the uptake of labelled sulphate in the Graafian follicles of the rabbit. Acta radiol. 39 (1953), 137.

FROM THE INSTITUTE OF RADIOPHYSICS, KING GUSTAF V JUBILEE CLINIC (DIRECTOR: PROFESSOR ROLF M. SIEVERT), STOCKHOLM, SWEDEN

A PROTECTION ARRANGEMENT FOR INTRACAVITARY RADIUM IN WARD PATIENTS

by

Rune Walstam

Measurements published on the radiation exposure of personnel engaged in radiologic work have shown that the highest doses (per week) are received by those employed in brachy-radium therapy (1, 2, 3).

This is especially the case in gynecologic radium treatment where high activities and long treatment times are used. It is possible to improve the technical arrangement of the packing and application to a rather satisfying level from the point of view of radiation protection, but it is very difficult to reduce the exposure that the ward personnel will receive during the treatment time. However, an arrangement that has decreased the ward exposure considerably was introduced at Radiumhemmet in 1952, and as it may be of general interest it is briefly described here.

In the Gynecologic Department at Radiumhemmet 5 grams of radium are used for intracavitary applications every week, the energy dissipated in the wards thus being equal to about 100 gram hours a week. Treatment times from seven up to thirty-five hours and applications of up to 350 mg radium in one patient are usual.

Dose measurements with condenser chambers (4) have given a mean value as high as 200—300 mr for the weekly exposure in the wards (where a staff of about fifteen are employed) although only the most urgent nursing is carried out.

Radiation measurements around patients with intracavitary radium for gynecologic treatment have shown a considerable body-absorption in certain directions.

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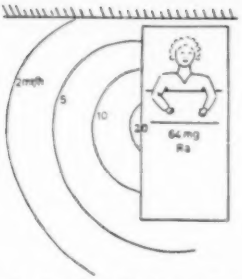

Fig. 1. Distribution of radiation around patient with 64 mg of radium in the uterus.

The dose distribution 1 m above the floor for a patient with 64 mg radium in the uterus is given in Fig. 1.

A more detailed measurement is described by MAYNEORD (3).

The dose distribution of course varies from case to case and is dependent on the position of the patient in the bed, but it may be seen that the dose rate at the head is lower than at the feet. This fact has been utilized in turning the bed to face the wall during the treatment time. The improvement in dose distribution is shown in Fig. 2 which illustrates the following advantages:

1) In the centre of the room the dose rate has decreased by 20—30 %.

2) Most of the nursing necessitates the nurse remaining close to the head of the patient. If A and B (in Fig. 2) represent the nursing position, the decrease in dose is about 50 %.

3) The card with the data of the patient is placed at the head of the bed and is easy to read from the centre of the room where the dose rate is not very high.

4) A bed that has been turned around immediately indicates that the patient is undergoing radium treatment.

The principal advantage in the dose distribution will of course be found about one meter above the floor, but for radiation of the whole body this level is the most important. The measurements described may thus be taken as an approximate measure of the advantages of the arrangement.

The first year's experience of the procedure at Radiumhemmet seems to have been satisfactory. Apart from the point of view of protection, nursing has been facilitated and it has also been found that turning the bed does not involve any increased discomfort for the patient during the period of treatment.

SUMMARY

The dose distribution is given around a patient with intracavitary radium for gynecologic treatment. A simple protection arrangement in wards for such patients is described and the advantages are shown through measurements.

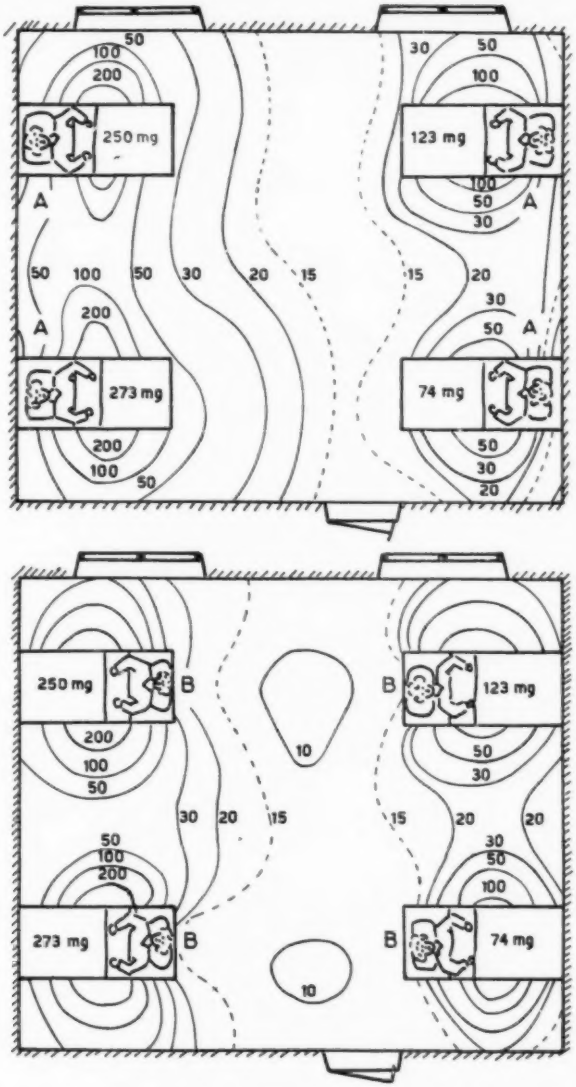

Fig. 2. Distribution of radiation in a room with four patients. The figure gives the amount of radium applied to each patient and the dose distribution in mr/h before and after turning the beds.

ZUSAMMENFASSUNG

Die Dosisverteilung in der Umgebung eines Patienten mit intrakavitärem Radium zur gynekologischen Behandlung wird besprochen. Eine einfache Massnahme zur Verbesserung des Strahlenschutzes wird angegeben und deren Vorteile durch Messungen gezeigt.

RÉSUMÉ

L'auteur donne la distribution des doses autour d'une malade en traitement gynécologique par curiethérapie intracavitaire. Il décrit un dispositif de protection simple dans les salles où sont ces malades et en montre les avantages par des mesures de doses.

REFERENCES

1. Bjerre Hansen, P. and Madsen, C. B.: Tolerance Dose Problems in Radiological Work. Acta radiol. 34 (1950), 519.
2. Klumpar, J.: Physical Aspects of Protection in Roentgen and Radium Therapy. Acta Radiol. o. Cancerol. Bohemoslov. 4 (1949), 152.
3. Mayneord, W. V.: Some Problems of Radiation Protection. Brit. J. Radiol. 24 (1951), 525.
4. Sievert, R. M. and Walstam, R.: Eine Methode für umfassende laufende Strahlenschutzmessungen. Fortschr. Röntgenstr. 75 (1951), 168.

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THE GAMMA-RAY DOSE IN CARCINOMA OF THE THYROID TREATED BY RADIO-IODINE

by

A. F. Phillips

The distribution of radio-iodine both in a normal thyroid gland and in a carcinoma of the thyroid capable of concentrating iodine is known to be irregular, and autoradiographic studies often show very intense foci of activity separated by relatively large areas with little or no activity. (HAMILTON, 1942; LEBLOND, 1943; MARINELLI et al., 1947; FRANTZ et al., 1948; FITZGERALD and FOOTE, 1949; PHILIPP, 1950; RAWSON and TRUNNELL, 1951; and others.)

In the case of the 8-day isotope I^{131}, by far the greater part of the ionisation within or close to an active region is due to the beta-rays, and these have very small penetrating power. The way in which the β-ray dose in tissue falls off with distance, has been measured or calculated by several authors, whose results do not appear to agree well (SIRI, 1949; ROSSI and ELLIS, 1950; MINDER and SCHINDLER, 1952; SOMMERMEYER, 1952). There is, however, no doubt that, even apart from geometrical factors due to the inverse square law, the dose is greatly reduced at a distance of 1 mm., and is negligible for therapeutic purposes at 2 mm., from a source of any shape. The gamma-rays on the other hand, cause relatively little ionisation, and have far greater penetrating power. Any point in a tumour receives an appreciable contribution of γ-radiation from all the radioactivity within some 30 cm radius. The possible importance of this in radio-iodine therapy has been mentioned by MARINELLI et al. (1947) and by RAWSON and TRUNNELL (1951). Regions of low activity would be unimportant in practice if they consisted entirely of necrotic or non-malignant tissue, but evidence will be presented that this is not always the case.

In a spherical mass with uniform distribution of activity, the dose is a maximum at the centre, and falls off, according to a curve which

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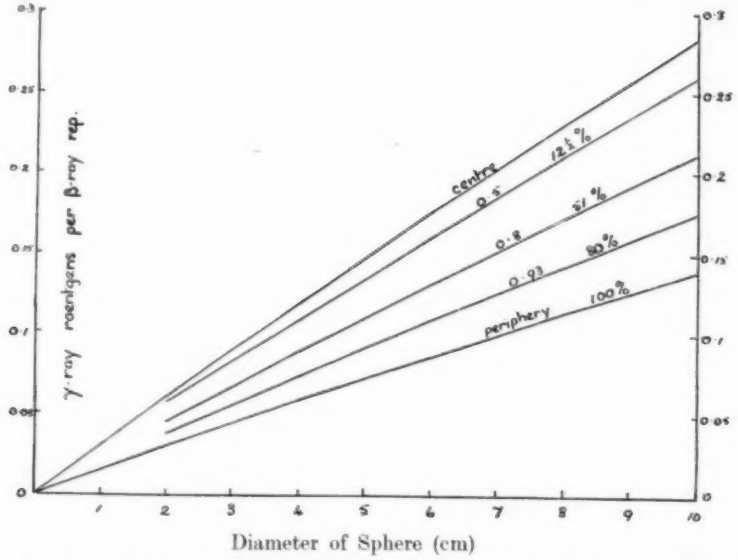


Ratio of γ-ray to β-ray dose in uniformly active spheres. I^{131}: $E_\beta = 0.20$ MeV, $K_\gamma = 2.25$ r/mC-hr at 1 cm., $\mu_\gamma = 0.03$. The numbers on the curves indicate the distance from the centre of the sphere expressed as a fraction of the radius, and the percentage of the total volume which lies within that distance from the centre.

depends upon the absorption coefficient, to approximately half this value at the periphery (MARINELLI et al., 1948; ODDIE, 1951). The relative contribution of the γ-rays to the dose in spheres of different diameters is shown in the diagram, which has been computed from ODDIE's formula. It is seen that only for very large tumours would the gamma-ray dose become a therapeutically useful addition to the β-ray dose, if the radioactivity were uniformly distributed.

The γ-ray dose is, however, far less affected by irregularities of distribution, and at regions of low activity surrounded by active regions the reduction would be expected to be small, even though the β-ray dose might fall practically to zero. The purpose of the experimental work reported here was to measure the actual γ-ray dose at points in tumours containing I^{131}, and in particular the dose at regions of low activity.

To give therapeutically useful γ-ray doses to such regions would require the administration of large amounts of I^{131}, and indeed might not be possible, because of the rapid excretion of doses which are large enough to cause severe radiation damage in the first day or two (FELLER et al., 1949), and because of the danger of damage to other organs. If the other

known isotopes of iodine can be made available in sufficient quantity, one may be found which is more suitable than I^{131} for treatment of carcinoma of the thyroid. For example, the 4-day isotope I^{124} emits β-rays (positrons) with 3 times the energy, which would penetrate approximately 4 times as far in tissue, and it also emits more energy as γ-rays per disintegration. Certain other isotopes emit only soft γ-rays and roentgen rays, with no β-rays.

Method of Measurement

Two operation specimens have been available in which thyroidectomy followed 2 days after a large tracer dose of radioiodine. Autoradiographs were made from slices of the tumours by placing them on roentgen film covered as usual by a folder of thin black paper within an envelope These showed the general distribution of activity within the tumours the beta-rays being the main source of photographic effect. Further autoradiographs were taken, using appropriately longer exposure times, with different thicknesses of absorbers of tissue-like material, the thinnest (2.4 mm. of celluloid) being thick enough to stop all the β-rays. Each roentgen film was calibrated by a range of three timed exposures to a collimated beam of β-rays from a 6 mgm. radium plaque held at a fixed distance. Development was done under controlled conditions, for which the radium exposures served as a check. Film densities were measured by means of a microscope and photo-electric cell, using uniform illumination over a square area (0.7 mm. side) on the film. The film sensitivity to the γ-rays from I^{131} was determined by exposure to a source of nominal strength 10 mC., at a distance of 50 cm., using the value 2.25 roentgens per millicurie hour at 1 cm. (BULLARD, 1952), under conditions of negligible back-scatter. The effect of a few millimetres of tissue-like material either in front of or behind the film was shown to be negligible. The accuracy of the 10 mC. source was confirmed by comparison with a standard source issued by the National Physical Laboratory, by means of a γ-ray Geiger counter, and this counter was also used to measure the activities of the operation specimens. The accuracy of these comparisons was somewhat better than the absolute accuracy of the standard source, namely ± 5 %.

Measurements of film densities were converted to γ-ray doses and plotted against thickness of absorber. The actual γ-ray dose at a point within the tumour was then calculated by adding the contributions of the several slices at the appropriate distances. The largest contributions were from the adjacent slices, for which extrapolation to zero absorber was necessary, and in the case of a region of low activity this was considered to be a reliable procedure to an accuracy of ± 10 %. Theoretical curves of intensity against distance for uniform active cylinders, cy-

lindrical shells, and other geometrical shapes, were calculated by means of the formulae of PARKER and SPIERS (MEREDITH, 1947), and compared with the curves obtained by measurement, to assist in this extrapolation.

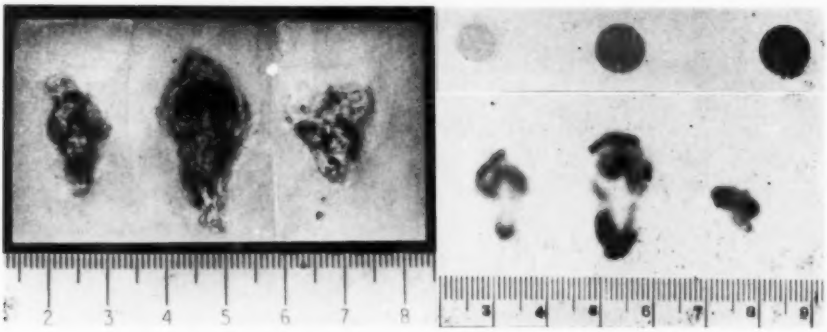
Material

Case 1, a man of 28, was a case of carcinoma of thyroid found inoperable two years previously and treated with I^{131} to a total of 140 mC. He had kept well, but lately had a recurrence in the right lobe of the thyroid and in lymph nodes on the right side of the neck. The B. M. R. was — 31 % and serum cholesterol 347 mgm/100 ml. A tracer dose of I^{131} was administered, and 14 % was found to be concentrated in the thyroid region and right side of the neck. No thyroid, iodine, or other relevant drugs had been administered for a considerable time, and no radiation in any form during the previous 20 months.

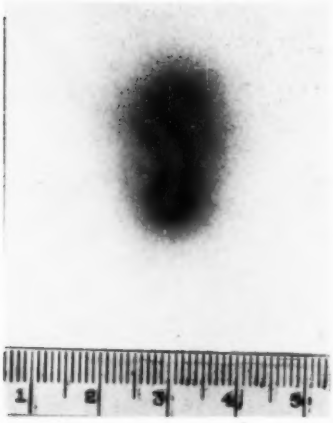
On 9/12/52, I^{131}, 25 mC., was given by mouth, and on 11/12/52 hemithyroidectomy was performed at Addenbrooke's Hospital (B. McN. TRUSCOTT), with resection of the greater part of the affected lymph nodes. The half thyroid and the lymph nodes were cut into slices 5 mm. thick, fixed in a 1 : 3 acetic acid/alcohol mixture, passed through alcohol and xylol, embedded in paraffin wax, and faced on the microtome. 15 % of the activity was extracted by the fluids. Sections were taken for histology and for microscopical autoradiographs by the stripping film technique (DONIACH and PELC, 1950). The pathological report (J. H. DEAN) was: "Appearances are consistent with acinar large cubical celled carcinoma of the thyroid with much oedema and degeneration of the stroma. Some of the acini contain eosinophilic colloid."

Post-operatively, 93 mC. of I^{131} was administered as a single therapeutic dose. At the time of writing (August 1953) the patient has been doing his usual heavy work for six months, and is symptom-free while taking 0.1 gm. of thyroid daily.

Case 2, a woman of 57, presented with a large goitre which had developed gradually over a period of one year, and was causing slight difficulty in respiration. There was radiographic evidence of metastases in the right lung field and in the right *os pubis*. On 2/3/53 she had I^{131}, 1.5 mC., by mouth, and the following day 3 % of the activity was present in the neck. A course of Lugol's iodine, 30 ml. in 16 days, had been finished only 3 days previously. On 9/3/53, with no further iodine administered, she was given a larger tracer dose of 25 mC., of which 4 % was present in the neck region on the following day. No uptake was demonstrated in the known metastases or elsewhere. On 11/3/53, the whole tumour in the neck, with the remains of the thyroid gland, was excised in one piece (J. E. ROWLANDS) at Newmarket General Hospital. The weight fresh was 164 gm., and a plaster model was made before any shrinkage had occurred. The specimen was divided into a smaller mass which had lain to the right of the trachea, containing the thyroid and a small part of the carcinoma, and a larger mass which had lain to the left of the trachea, containing most of the primary tumour and (by autoradiographic evidence) a very little thyroid tissue. The larger mass was divided into 5 slices approximately 1 cm. thick, and the smaller into 3 pieces. The slices were too large to be conveniently embedded in paraffin wax at once, and the autoradiographs required for γ-ray measurements were taken while the slices were allowed to dry from xylol. Subsequently they were embedded and faced up, for beta-ray autoradiographs. 5 % of the activity was extracted in fixation and dehydration. The tissue shrank during these processes, the linear dimensions being reduced by 27 %; this has been allowed for in calculating the γ-ray doses.



a. b.



c.

Fig. 1. Case 1. Primary tumour.

a. Slices embedded in paraffin wax, with scale of centimetres.

b. β-ray autoradiographs, and film calibration spots.

c. γ-ray autoradiograph of central slice: absorber 2.4 mm. of celluloid; exposure 10 times that of Fig. 1 b.

The pathological report (J. H. Dean) was: "small acinar and tubular cubical celled carcinoma of thyroid".

A month after operation, a tracer dose of radio-iodine showed concentration in a metastatic deposit in the right tibia. A course of 100 mC. of I^{131} was then given in 4 equal weekly doses. Four months after operation selective uptake was still present in the right tibia. A small lump in the neck was not increasing in size, and the pulmonary and pubic metastases were less evident radiologically. The patient was free of symptoms without thyroid medication. A second course of 100 mC. of I^{131} was started at this time.

Results

Case 1. The embedded slices of the primary tumour, and the corresponding β-ray autoradiographs, are reproduced in Fig. 1. There was a central region of very low or zero activity, surrounded by a shell of

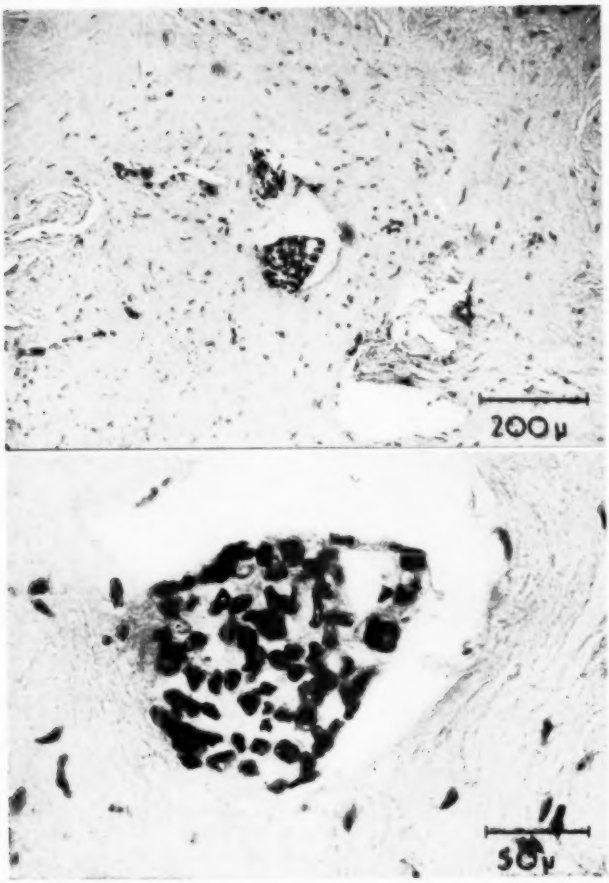


Fig. 2. Case 1. Primary tumour. Photomicrographs of an isolated group of cells surrounded by inactive fibrous tissue. Haematoxylin and eosin. a. × 80. b. × 320.

active tissue. The inactive region on the central slice measured 12 × 3 mm., and the thickness of it was too great to allow any effective β-radiation to reach its centre. Histologic examination of stained sections showed a broad correlation with the autoradiographic appearance, the central area being mainly composed of fibrous tissue and the active rim of more or less differentiated carcinoma, with plentiful stroma. A point of particular interest, however, was the presence of a few groups of carcinoma cells

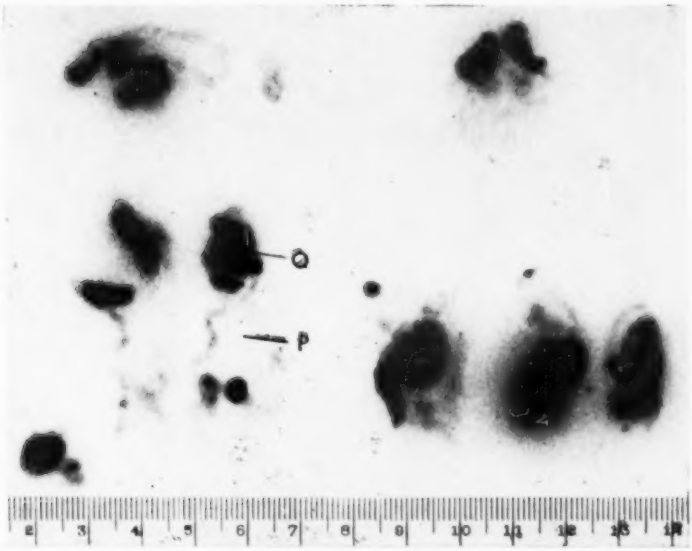


Fig. 3. Case 1. Lymph node metastases. β-ray autoradiographs. P, Q are the points selected for γ-ray dose determination. (The outlines of the slices are shown up by an artefact.)

within the fibrotic core and out of effective range of β-rays from the active shell (Fig. 2). These groups of cells did not themselves show appreciable uptake of radio-iodine in the microscopical autoradiographs. Although the cells were apparently surrounded by fibrous tissue, they had survived for at least 20 months after the last treatment by radiation, and therefore must be regarded as viable and potentially malignant.

γ-ray autoradiographs were taken through a number of different absorbers from 2.4 mm. to 25 mm. in thickness; an example is reproduced in Fig. 1 C. The total γ-ray dose at the centre of the exposed face of the central slice has been calculated by the method described (see Table 1).

The radioactivity in the lymph node metastases was very irregularly distributed, as was shown by the β-ray autoradiographs (Fig. 3), the highest concentrations being approximately equal to those in the primary tumour. The gamma-ray doses have been determined for a region of low activity near the centre, and for one of high activity near one edge, of the main mass: they differ by less than a ratio of 1 : 2.

Histologically there was again a broad correlation between the activity and the type of tissue, but the regions of low activity (apart from the cyst

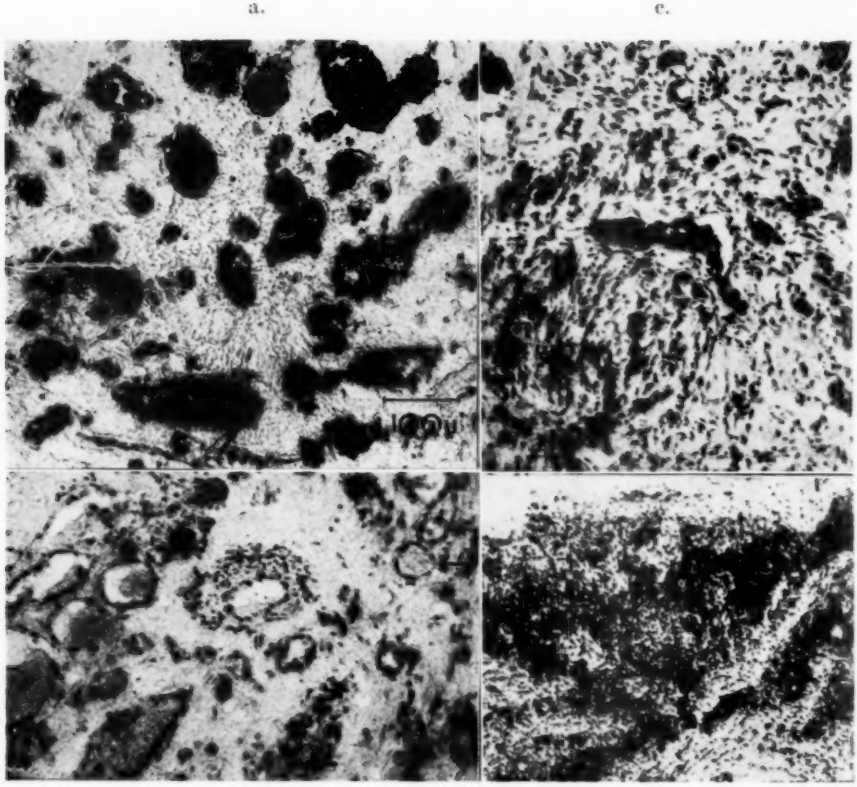
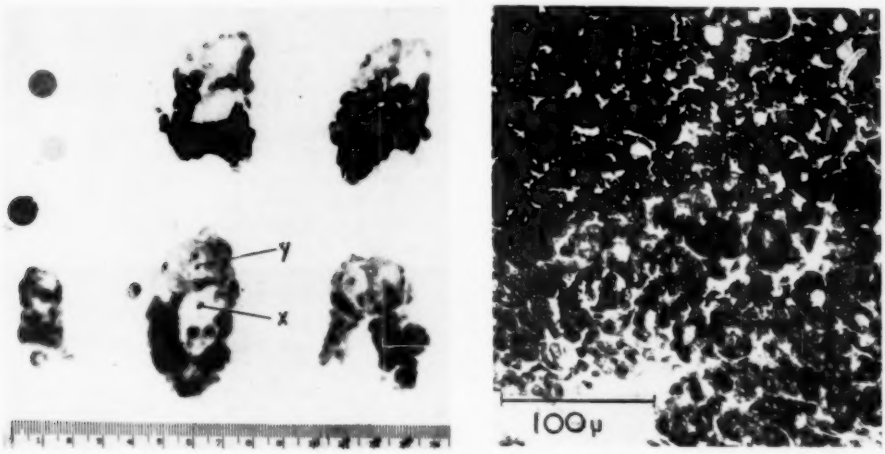


Fig. 4. Case 1. Lymph node metastasis. Stripping film autoradiographs superimposed on sections, showing great variation of histology and of radioactivity within a single tumour. Magnification approx. × 100 in all cases. Haematoxylin and eosin. a. Follicle formation with good uptake of I^{131}. b. Follicle formation with very variable uptake: note two small follicles (marked by arrows) which contain colloid but give no autoradiograph. c. Partially differentiated carcinoma with no uptake. d. Undifferentiated carcinoma invading lymphoid tissue. No uptake.

of which the fluid contents escaped before fixation) corresponded sometimes with fibrous or necrotic tissue, sometimes with less differentiated carcinoma cells. Microscopical autoradiographs showed the usual spotty concentration in regions where there was follicle formation: most, but not all, follicles containing colloid gave a dense autoradiograph (Fig. 4).



a. β-ray autoradiographs. X, Y are the points selected for γ-ray dose determination.

b. Photomicrograph of section from region Y. Haematoxylin and eosin.

Fig. 5. Case 2. Primary tumour.

Case 2. The displaced surviving part of the thyroid was histologically normal, and gave a dense autoradiograph.

The β-ray autoradiographs of the slices of the primary tumour are reproduced in Fig. 5. There were regions of low uptake up to 12 mm. in diameter. γ-ray autoradiographs were taken as before, and two points were selected in regions of low activity, marked X and Y in the figure, for calculation of the γ-ray dose (see Table 1). Histological examination of small blocks subsequently removed from these positions in the specimen showed mainly necrotic tissue from region X, but region Y consisted of densely cellular alveolar carcinoma, with traces of colloid in places (Fig. 5 b). There was a small uptake of I^{131} in region Y, sufficient to give a β-ray dose of the same order of magnitude as the measured γ-ray dose. In region X there was no measurable uptake of I^{131}.

The last column of the Table shows the theoretical γ-ray dose at the centre of spheres or ellipsoids of revolution of the same volume as the different specimens, and containing the same total activity uniformly distributed. These are of the same order of magnitude as the doses measured for the regions of low activity.

Conclusions

It is generally considered that radical radiotherapy requires a certain minimum dose of radiation to be delivered to every part of the tumour.

Table 1

Calculated β- and γ-ray doses of radiation and measured γ-ray doses

In each case 25 mC. of I^{131} was given by mouth two days before operation. The activities are referred to the day of operation, and all doses are quoted as those due to complete radioactive decay of the activity present on that day. Both the effect of excretion, and the radiation delivered between administration of the radio-iodine and the time of operation, are neglected. The measured doses are corrected for loss in the fixing fluids, and the appropriate correction has been made for shrinkage in Case 2. In Case 1, the shrinkage was not measured, and no correction has been applied: it is possible that the measured doses should be reduced by 30 %.

Specimen	Weight (grams)	Total Activity (μC)	Specific Activity (μC/gm)	Calc. mean β-ray dose (rep)	Measured γ-ray dose		Calc. γ-ray dose at centre of figure of equal volume
					region	roentgens	
Case 1							
Primary tumour	5.0	207	41	5,200	centre	400	340 (sphere)
Metastasis	13.5	127	9.4	1,200	P (Fig. 3)	100	100 (ellipsoid)
					Q (Fig. 3)	180	
Case 2							
Larger mass (carcinoma)	139	190	1.4 [1]	175 [1]	X (Fig. 5)	24	34 [1] (sphere)
					Y (Fig. 5)	21	
Smaller mass	25	366	14.6	1,850			210 (sphere)
Thyroid tissue (estimated)	13	349	26.8	3,400	Maximum	420	280 (ellipsoid)

[1] These figures are raised because of a small amount of thyroid tissue with high activity at one edge of the tumour.

This object would not have been achieved by the β-rays of radio-iodine in either of the cases investigated, even if very large amounts of I^{131} had been employed, because some viable cells lay further than the maximum range of the β-rays from any region where there was considerable uptake. Others lay in regions where absorption reduced the dose to a small fraction of the theoretical mean dose.

The γ-rays delivered a dose of radiation which, although in active regions much smaller than the β-ray dose, was relatively little affected by irregularities of distribution of the type found. This was the main form of radiation reaching those regions which did not themselves take up radio-iodine. The γ-ray doses measured in the lowest regions were not very different from those calculated for uniform distribution of radioactivity. It would, however, have required the administration of very large amounts of radio-iodine in order to have achieved a therapeutically useful γ-ray dose in the less active of the specimens in each case. In some cases, at least, such large amounts would certainly be impracticable.

The possibility of using other radioactive isotopes of iodine needs to be explored with the object of giving more radiation to regions of low activity, either by means of more energetic β-rays which have longer ranges in tissue, or by means of an isotope giving a higher ratio of γ-ray dose to β-ray dose.

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SUMMARY

The irregular distribution of radioactive iodine taken up by carcinoma of the thyroid, and the short range of the beta-rays emitted by I^{131}, appear likely to leave certain regions of the tumours virtually unirradiated by these rays. The dose of radiation in such regions due to the gamma-rays from I^{131} has been measured in operation specimens from two cases, and was found to be of the same order of magnitude as the dose calculated for uniform distribution of the radioactivity. Malignant cells were present in some of the regions of low activity. In general it may be impossible to give large enough gamma-ray doses by means of I^{131} to effect a cure. Other radioactive isotopes of iodine may prove more useful in the treatment of carcinoma of the thyroid.

ZUSAMMENFASSUNG

Die unregelmässige Verteilung von radioaktivem Jod im Schilddrüsenkrebsgewebe und die kleine Reichweite der von I^{131} ausgegebenen-β-Strahlen mag gewisse Regionen des Tumors in Wirklichkeit unbestrahlt lassen. In derartigen Regionen ist die Strahlendosis, die den γ-Strahlen von I^{131} entstammt, am Operationsmaterial von zwei Fällen gemessen worden; es wurde gefunden, dass sie vom derselben Grössenordnung ist wie die für gleichmässige Verteilung der Radioaktivität errechnete Dosis. Bösartige Zellen sind in einigen Regionen mit geringer Radioaktivität gefunden worden. Im allgemeinen scheint es unmöglich zu sein, mittelst I^{131} genügend grosse Dosen von γ-Strahlen zu applizieren, die eine Heilung bewirken. Andere Radioisotope des Jod mögen sich als brauchbarer in der Behandlung des Schilddrüsenkrebses erweisen.

RÉSUMÉ

La distribution irrégulière d'iode radioactif, fixé dans les tissus cancéreux de la thyroïde et le parcours rélativement court des rayons β, émis par I^{131}, peut, en réalité, laisser certaines régions des tumeurs non-irradiées par ces rayons. Ici la dose de radiation, dûe aux rayons γ (émis par I^{131}), a été déterminée dans des échantillons, obtenus par opération de deux cas. La dose trouvée et la dose calculée à base de distribution uniforme de radioactivité, étaient du même ordre de grandeur. Des cellules malignes étaient présentes dans quelques régions à basse radioactivité. En général il semble être impossible d'appliquer des rayons γ, émis par I^{131}, en doses suffisantes pour obtenir une guérison. Il se peut que d'autres isotopes radioactifs d'iode donnent des résultats plus avantageux dans le traitement des cancers de la thyroïde.

REFERENCES

BULLARD, E. C.: British Standard of radioactive iodine (I^{131}). Nature 170 (1952), 916.

DONIACH, I., & PELC, S. R.: Autoradiographic technique. Brit. J. Radiol. 23 (1950), 184.

FELLER, D. D., CHAIKOFF, I. L., TAUROG, A. & JONES, H. B.: The changes induced in iodine metabolism of the rat by internal irradiation of its thyroid with I^{131}. Endocrinology 45 (1949), 464.

FITZGERALD, P. J. & FOOTE, F. W.: The function of various types of thyroid carcinoma as revealed by autoradiographic demonstration of I^{131}. J. Clin. Endocrinol. 9 (1949), 1153.

FRANTZ, V. K., QUIMBY, E. H. & EVANS, T. C.: Radioactive iodine studies of functional thyroid carcinoma. Radiology 51 (1948), 532.

HAMILTON, J. G.: The use of radioactive tracers in biology and medicine. Radiology 39 (1942), 541.

LEBLOND, C. P.: Localisation of newly administered iodine in the thyroid gland as indicated by radio-iodine. J. Anat. 77 (1943), 149.

MARINELLI, L. D., FOOTE, F. W., HILL, R. F., & HOCKER, A. F.: Retention of radioactive iodine in thyroid carcinomas. Histopathologic and radio-autographic studies. Am. J. Roentgenol. 58 (1947), 17.

MARINELLI, L. D., QUIMBY, E. H., & HINE, G. J.: Dosage determination with radioactive isotopes. Nucleonics 2: 4 (1948), 56.

MEREDITH, W. J. (Ed.): Radium dosage: The Manchester System. Livingstone, Edinburgh 1947.

MINDER, W., & SCHINDLER, H.: Die Strahlungverteilung einer homogen mit radioaktiver Substanz gefüllten Kugel. Strahlentherapie 86 (1952), 602.

ODDIE, T. H.: Dosage from radioisotopes uniformly distributed within a sphere. Brit. J. Radiol. 24 (1951), 333.

PHILIPP, K.: Anwendung radioaktiver Isotope in der Medizin. Strahlentherapie 83 (1950), 51.

RAWSON, R. W., & TRUNNELL, J. B., writing in A Manual of Artificial Radio Isotope Therapy, Ed. Hahn, P. F., Acad. Press Inc., New York 1951.

ROSSI, H. H. & ELLIS, R. H.: Distributed beta sources in uniformly absorbing media. Nucleonics 7: 1 (1950), 18.

SIRI, W. E.: Isotopic tracers and nuclear radiations. McGraw Hill, New York 1949, p. 58.

SIRI, W. E.: Personal communication quoted by Feller et al. (1949).

SOMMERMEYER, K.: Beiträge zur Dosierung der β-Strahlung radioaktiver Substanzen, Strahlentherapie 88 (1952), 329.

DU CENTRE ANTI-CANCÉREUX DE L'UNIVERSITÉ DE LIÈGE, BELGIQUE

INFLUENCES DU MODE D'IRRADIATION, DE L'HYPOPHYSECTOMIE, DES HORMONES GONADOTROPES ET DES RADIO-PROTECTEURS CHIMIQUES SUR LA REPONSE DE L'OVAIRE DE LAPINE AUX RAYONS RÖNTGEN

par

Paul Desaive

L'irradiation röntgenienne expérimentale d'un organe à fonctionnement cyclique comme l'ovaire peut être réalisée soit en une fois, soit en répartissant la dose choisie sur plusieurs séances, dont la somme des durées particulières est égale à la durée de l'irradiation unique.

La comparaison des résultats obtenus, par l'un et l'autre de ces deux modes — massif et fractionné — d'irradiation, sur un substrat biologique déterminé, permet d'analyser entre autres phénomènes, le comportement des processus dits de restauration, à l'étude desquels P. LAMARQUE s'est particulièrement consacré.

Si la réparation intervient après chaque séance d'irradiation, il est évident que, *sur un matériel biologique absolument stable*, la dose de rayons röntgen administrée par fractions doit être supérieure à la dose donnée en une fois, si l'on veut obtenir dans les deux cas le même effet destructeur.

Il n'entre pas dans nos intentions de discuter ici la question si intéressante de la restauration post-röntgenienne. Mais, ayant observé au cours d'études antérieures (DESAIVE 1940) sur l'ovaire irradié de lapine adulte, que le rendement obtenu au niveau de l'appareil folliculaire était meilleur, tant du point de vue de la destruction intégrale de ce système que de celui de la stérilisation de l'animal (effet qui n'exige pas nécessairement la disparition histologique de tous les follicules primordiaux), lorsque la dose était répartie en plusieurs fractions journalières successives au

Soumis à la Réd. le 3 Septembre, 1953.

lieu d'être donnée en une fois, nous avons cherché à démontrer que cette anomalie apparente était vraisemblablement la conséquence d'une variation importante de la radio-sensibilité folliculaire pendant la période d'irradiation.

Dans ce but, nous avons comparé les effets ovariens d'une dose donnée de rayons röntgen et ceux de la même dose administrée par fractions, avec les résultats obtenus après préparation de l'animal par une action modificatrice de la radio-sensibilité ovarienne ou générale.

Matériel et techniques

Nous avons utilisé des lapines adultes d'un poids moyen de 2 kilos. Ces animaux ont été isolés en cage, un mois au moins avant le début des expériences, et soumis à un régime alimentaire identique.

L'irradiation a toujours porté, par voie lombaire, sur le seul ovaire droit, l'animal étant solidement fixé sur le ventre; le tube a été centré sur le flanc droit, à 2.5 cm. de la ligne des apophyses épineuses et sur une droite transversale passant à mi-distance entre la dernière côte et l'apophyse iliaque antéro-supérieure; l'ovaire gauche et le reste de l'animal ont été protégés par des caches en plomb. Les conditions physiques de l'irradiation ont été choisies comme suit:

Tension:	165 kilovolts
Intensité:	4 milliampères
Filtration:	5 mm aluminium
Distance focale:	28 cm.

Dosage à la peau par dosimètre Hamer ou Mékapion.

Après l'irradiation, les animaux ont été isolés jusqu'au moment choisi pour le prélèvement des ovaires. Ceux-ci ont été fixés au Bouin ou au Hollande, inclus dans la paraffine, coupés en série à 5 μ et colorés par l'hématoxyline-éosine ou l'hémalun-picro-ponceau.

Les coupes ont été dessinées, à la moyenne de 1 sur 10, au projecteur (SIP) (Genève) et les follicules numérés par une technique que nous vous avons décrite ailleurs (Desaive 1940).

Schémas expérimentaux

Nous avons exécuté deux groupes d'expériences, répondant aux buts suivants:

1. Détermination des seuils de stérilisation et de destruction du système folliculaire de la lapine adulte

A. Lacassagne, dans une remarquable étude de l'ovaire irradié de la lapine a démontré que la destruction de l'appareil folliculaire de cet

organe ne pouvait être affirmée qu'après 4 à 5 mois d'observation: cette longue latence est nécessaire à la remise en train des follicules primordiaux qui n'ont pas été immédiatement détruits par les rayons röntgen ou n'ont pas succombé à des lésions latentes lors de leur entrée en évolution.

Après avoir préalablement établi que, dans les conditions physiques que nous avons choisies, une dose de 1,250 r était incapable de détruire complètement l'appareil folliculaire, mais que ce résultat était régulièrement obtenu par une dose de 3,250 r, quel que soit le mode (massif ou fractionné) de l'administration de cette quantité de rayons röntgen, nous avons préparé nos animaux de la manière que voici:

a) 20 lapines ont reçu sur l'ovaire droit, en une seule application, des doses respectives de 1,750, 2,000, 2,250, 2,500, 2,750 et 3,000 r internationaux.

b) 19 lapines ont reçu sur l'ovaire droit, des doses respectives de 1,750, 2,000, 2,250, 2,500, 2,750 et 3,000 r, réparties en cinq applications journalières successives de 350, 400, 450, 500, 550 et 600 r internationaux.

Dans l'une et l'autre de ces deux classes, 6 animaux (1 pour chacune des six doses choisies) ont été sacrifiés le 100e jour après l'irradiation, 6, le 130e jour, et 6, le 160e jour; nous avons quelquefois réservé deux lapines pour une dose et une durée identiques.

L'ovaire droit a été débité en coupes sériées, de même que l'ovaire gauche témoin.

Chacun des ovaires étudiés à fait l'objet d'une numération détaillée, suivant une technique personnelle, de tous les éléments folliculaires qu'il contenait, classés en 8 types histologiques: P (follicule primordial); A, B, C et D (follicules témoins des phases successives de la croissance ovocytaire); E, F et G (follicules cavitaires représentant les stades évolutifs qui correspondent à l'action gonadotrope de la préhypophyse).

2. Recherche de l'influence de diverses actions modificatrices de la radiosensibilité folliculaire sur le comportement de l'appareil noble de l'ovaire vis à vis des rayons röntgen

Nous avons mis en œuvre les trois systèmes modificateurs suivants:

a) Destruction de l'hypophyse

Pour rendre nos lapines hypophyséoprives, nous avons employé chez 12 animaux, soit la technique par implantation intra-sellaire de Radon, mise au point par Lacassagne et Nyka, (7 cas), soit une technique personnelle d'introduction dans la selle turcique d'un tube capillaire rempli de quinine-urée (scléro-serum) (5 cas). L'irradiation de l'ovaire droit a été exécutée au moins 30 jours après l'intervention sur l'hypophyse.

Nous n'avons considéré comme hypophyséoprives que les animaux chez lesquels nous avons pu vérifier, à l'examen histologique, des lésions définitives de la pituitaire. Comme cette vérification n'a, bien entendu, été faite qu'après avoir sacrifié nos lapins irradiés, nous avons classé nos expériences en deux catégories: dans la première, nous avons fait rentrer 6 animaux hypophyséoprives, et dans la seconde 6 lapines dont l'hypophyse n'avait subi que des altérations partielles.

Les animaux hypophyséoprives ont succombé entre le 18e et le 104e jour après l'irradiation; ceux dont l'hypophyse n'était atteinte qu'incomplètement, ont été sacrifiés le 150e jour.

Dans le groupe intégralement hypophyséoprive, les doses de rayons röntgen, administrées en une seule application, ont été de 1,750, 2,000, 2,250, 2,500 et 2,750 r (deux cas).

Dans le groupe partiellement hypophyséoprive, les doses de rayons röntgen données, également en une seule séance, ont été de 1,750, 2,000, 2,200, 2,400, 2,500, et 2,600 r.

b) *Préparation par des gonadotrophines*

Nous avons employé une gonadotrophine chorionique (le Prolan Bayer), à dose faible — 400 unités Rat en 4 injections journalières successives de 100 unités Rat (20 lapines) ou à dose élevée — 2,700 unités Rat, en 9 injections journalières successives de 300 unités Rat (12 lapines). La gonadotrophine a été introduite par la veine marginale de l'oreille, et l'irradiation a commencé le lendemain de la dernière injection intraveineuse.

L'irradiation a été faite en une seule application de 1,250, 1,500, 1,750, 1,850, 2,000, 2,250, 2,500 ou 2,750 r.

Les animaux ont été sacrifiés: dans la première série: 6 le 100e jour (doses de 1,500, 1,750, 2,000, 2,250, 2,500, 2,750 r), 6 le 130e jour (après les mêmes doses) et 8 le 160e jour (après les mêmes doses); et dans la seconde série: 6 entre le 85e et le 120e jour (doses de 1,500, 1,750, 1,850, 2,000, 2,250 et 2,500 r) et 6 le 160e jour (doses de 1,250, 1,500, 1,750, 2,000, 2,250 et 2,500 r).

c) *Préparation par un radio-protecteur chimique*

Nous avons utilisé, sur 22 lapines, la β-mercapto-éthylamine (corps 1,573 — Labaz), étudié à Liège par Z. M. Bacq et ses collaborateurs et sur 2 lapines le cyanure de potassium.

Le protecteur, à la dose de 1 mmg. par kilo pour le cyanure (en moyenne, 2 mmg.) et de 25 mmg. par kilo (en moyenne 50 mmg.) pour le 1,573 L, a été injecté dans la cavité péritonéale, immédiatement avant l'irradiation, la lapine étant fixée sur son support, sous l'ampoule de rayons röntgen.

Nous avons réparti ces 24 lapines en deux groupes.

Dans le premier, nous avons utilisé la technique d'irradiation massive avec des doses de 1,750, 2,000, 2,250, 2,500, 2,750 et 3,000 r; les prélèvements ont été faits soit après des délais courts: du 45e au 91e jour (5 lapines irradiées à 1,750, 2,000, 2,250, 2,500 et 2,750 r) soit après des délais longs: du 122e au 137e jour (6 lapines irradiées à 2,000, 2,250, 2,500, 2,750, 2,750 et 3,000 r).

Dans le second, nous avons réparti les doses choisies (de 1,750 à 3,000 r) en 5 fractions égales, administrées en 5 jours successifs (soit 5 fois 350, 400, 450, 500, 550 et 600 r); et avant chaque séance, les lapines ont reçu une dose de 1,573 L. identique à celle utilisée pour les applications à dose massive; les prélèvements ont été faits soit après des délais courts: entre le 53e et le 95e jour (6 lapines irradiées à 1,750, 2,000, 2,250, 2,500, 2,750 et 3,000 r), soit après des délais longs (entre le 122e et le 137e jour) (7 lapines irradiées à 1,750, 2,000, 2,250, 2,500, 2,750, 2,750 et 3,000 r).

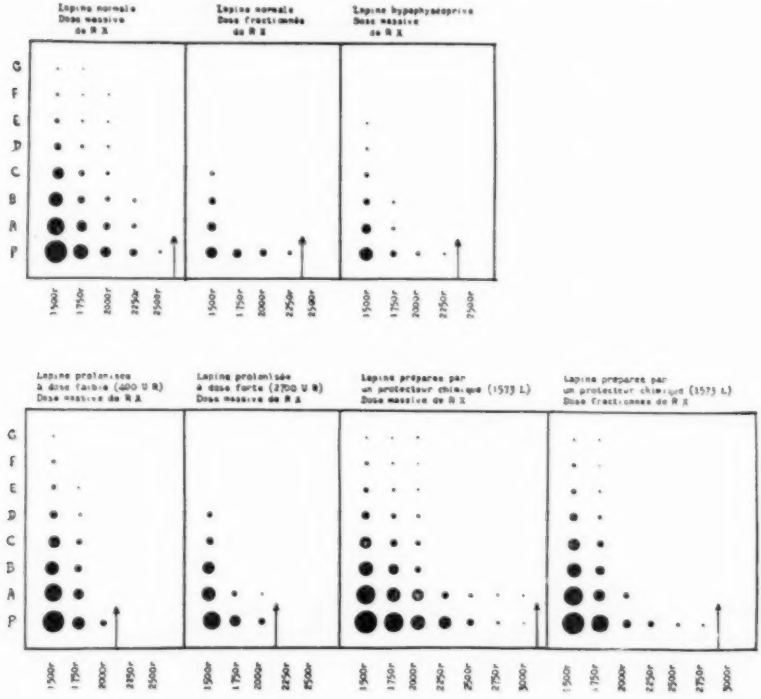
Etude des résultats obtenus

Pour faciliter la comparaison des effets de l'irradiation sur l'ovaire droit des lapines de nos différents groupes expérimentaux, nous avons construit le schéma ci-joint.

Ce dernier comprend 7 cases réservées aux 7 principaux thèmes d'expérience que nous avons pratiqués, à savoir l'irradiation à dose massive, l'irradiation à dose fractionnée, l'irradiation massive après hypophysectomie, l'irradiation massive après prolanisation à dose faible ou élevée, et enfin l'irradiation massive ou fractionnée après protection; nous avons limité les indications de ce schéma aux seuls prélèvements *à long terme* (l'irradiation après hypophysectomie exceptée).

Dans chacune de ces sept cases sont tracés les deux axes cartésiens: en abcisses, se trouvent les doses croissantes utilisées, et en ordonnées, les stades successifs des follicules ovariens (de P à G); en regard d'une dose donnée la succession verticale (et décroissante de bas en haut) de cercles pleins, indique des «présences» de follicules d'un type déterminé. Les cercles n'ont pas de dimensions exactement proportionnelles aux nombres de follicules présents à chacun des stades considérés; ils indiquent simplement que les follicules aux stades desquels ils correspondent sont présents dans l'ovaire. Pour que la répartition numérique puisse être reflétée par des cercles de dimensions comparables d'un ovaire à l'autre, il faudrait que les nombres de follicules présents à chaque stade, au départ de l'expérience, soient identiques dans tous les ovaires étudiés: il ne peut en être ainsi. Le fait important n'est d'ailleurs pas que l'ovaire x, irradié à 2,000 r contienne plus de follicules C, par exemple, que l'ovaire y, irradié à 1,750 r, mais que cet ovaire x ne renferme que des follicules

Evolution folliculaire après irradiation (Etat à partir du 130e jour)



P, A, B, et C alors que l'ovaire y montre une évolution folliculaire plus poussée, atteignant, par exemple, le stade E.

Lorsque la série est complète ou presque (de P à G ou F) on peut considérer que l'ovaire a repris une évolution normale; lorsqu'elle s'arrête aux stades D ou E, on est en droit d'admettre que l'ovaire n'est pas encore capable de répondre à la sollicitation préhypophysaire; lorsqu'elle n'atteint que les stades A ou B, c'est que les follicules en cours sont issus de formes primordiales gravement atteintes par l'irradiation; si les seuls follicules primordiaux sont représentés, on peut affirmer (entre le 130e et le 160e jour), que l'ovaire est stérilisé; enfin, s'il n'existe plus aucun follicule perceptible, on doit admettre que l'appareil folliculaire est complètement détruit.

Notons en passant que même dans ce dernier cas, nous n'avons jamais décelé de lésions de l'épithélium germinatif et pas davantage de bourgeonnements néoformateurs de follicules à partir de ce dernier. Dès lors, il

nous paraît improbable que le cortex ovarien — chez la lapine tout au moins — soit à même d'assurer des générations post-pubertaires de follicules primordiaux, fait négatif sur lequel nous avons insisté précédemment (DESAIVE 1941).

L'examen de ce schéma autorise les conclusions suivantes:

1er Groupe expérimental. — Détermination des seuils de stérilisation et de destruction röntgenienne de l'ovaire

Dans les conditions physiques que nous avons choisies, il nous est apparu qu'une seule application de 2,500 r (mesurée à la peau) suffit à assurer la stérilisation de la lapine, et dans la majorité des cas, la destruction de l'appareil folliculaire. Sous irradiation massive, l'ovaire a une activité pratiquement normale jusqu'à 2,000 r; et à 2,250 r, la stérilisation est obtenue une fois sur deux.

Si nous fractionnons la dose, nous observons encore des follicules primordiaux, en nombres décroissants, de 1,750 jusqu'à 2,250 r; à partir de 2,500 r il n'en existe habituellement plus; les rares éléments qui persistent dans certains cas sont vraisemblablement lésés de manière définitive; mais — différence énorme d'avec l'irradiation à dose massive — souvent après 1,750 r et, à coup sûr à partir de 2,000 r, l'ovaire ne montre plus aucune évolution folliculaire!

Le fractionnement de la dose réalise donc la stérilisation à partir de 2,000 r; mais il n'assure la destruction folliculaire qu'entre 2,250 et 2,500 r. L'interprétation de cet accroissement des effets des rayons röntgen par le fractionnement et l'étalement de la dose doit naturellement être basée sur le caractère cyclique de l'évolution folliculaire et vraisemblablement sur des variations corrélatives de l'indice de radiosensibilité des follicules primordiaux.

Nous reviendrons ultérieurement sur cet aspect du problème que nous nous sommes posé.

2ème groupe expérimental. — Etude du comportement vis à vis des R. R. des ovaires soumis à des actions théoriquement modificatrices de leur radiosensibilité

a) *Lapines hypophyséoprives*

Nous n'insisterons pas sur les resultats obtenus chez des lapines à hypophyse partiellement conservée; chez ces animaux, les éléments préhypophysaires épargnés sont suffisants, semble-t-il, pour assurer une évolution folliculaire raisonnable; et les résultats de l'irradiation confirment, dans leur ensemble, ceux obtenus sur lapines normales massivement irradiées.

La destruction complète de l'hypophyse a pour effet essentiel, au

niveau de l'ovaire, la suppression du développement folliculaire au delà du stade E; la composition numérique des différents stades persistants cesse d'être soumise à des variations cycliques et se maintient à un niveau comparable à celui qu'elle atteint, dans tout ovaire normal, peu après son passage par la zone d'activité ovocytaire maxima. L'ovaire de lapine hypophyséoprive est donc ramené à la seule phase autonome de son évolution folliculaire; les taux de follicules A, B, C, D et E qu'il contient encore deviennent pratiquement constants; et l'état stable qu'il acquiert ainsi se situe, sur le tableau numérique de l'évolution folliculaire, au voisinage immédiat de la transition: phase folliculaire — phase paralutéinique (DESAIVE 1949).

Il est clair, que dans ces conditions, l'ovaire doit avoir une radiosensibilité très stable, à tous les étages de son appareil folliculaire. C'est ce qui explique la régularité des résultats que nous avons obtenus dans la présente expérience, et qui se rapprochent de ceux que nous a fournis l'irradiation fractionnée et étalée de l'ovaire de lapine normale, puisque dans les deux cas la dose de stérilisation se situe entre 1,750 et 2,000 r, et la dose destructrice, entre 2,500 et 2,750 r.

Cette expérience est toutefois entachée d'une cause d'erreur, qui tient à la difficulté de maintenir longtemps en vie des lapines hypophyséoprives, fait qui ne nous a pas permis d'établir, si, au 160e jour, certains follicules primordiaux auraient été ou non capables de reprendre leur évolution. Dans le doute, nous admettrons — jusqu'à confirmation ultérieure — que l'hypophysectomie rend l'ovaire plus radio-sensible, à la faveur de l'extrême régularité de ses processus — autonomes — de production de follicules évolutifs, regularité qui présuppose une certaine constance dans le comportement métabolique des ovocytes primordiaux et par conséquent, dans la radio-sensibilité de ceux-ci.

b) *Lapines gonadotropisées*

L'ovaire répond à la sollicitation, par le prolan, de ses éléments ultra-E d'abord en portant l'ensemble de son effectif folliculaire à un niveau voisin de celui qu'il atteint normalement à la fin de la phase folliculaire, correspondant à ses possibilités maxima en follicules G, ensuite en s'efforçant de maintenir l'équilibre, d'ailleurs instable, ainsi réalisé, pendant toute la période d'efficacité du principe gonadotrope, c'est à dire pendant 9.56 jours, tout au plus.

Il n'est pas aisé d'apprécier les conséquences qu'une modification de ce genre au rythme ordinaire de la vie ovarienne peut avoir sur l'avenir de l'organe: mais il est permis d'émettre, à priori, l'hypothèse que l'ovaire, dans les premiers jours de la prolanisation, doit être plus sensible aux agents modificateurs externes, et notamment aux rayons röntgen; et les premières recherches que nous avons entreprises à ce propos semblent

nous autoriser à considérer le prolan comme un radiosensibilisateur ovarien spécifique (DESAIVE 1949).

Les deux expériences actuelles confirment en tous points cette supposition, et démontrent, en outre, que l'effet radio-sensibilisant de la gonadotrophine est fonction directe de la dose employée de ce produit.

En effet, avec 400 unités Rat, l'ovaire irradié présente encore, sous 1,750 r, une évolution continue jusqu'au stade E; mais sous 2,000 r, la stérilisation est obtenue, et à partir de 2,500 r, la glande ne renferme plus un seul follicule P.

Avec 2,700 unités Rat, à 1,250 r déjà, se montre un freinage important du développement folliculaire, qui est arrêté au stade B; à partir de 1,750 r, il n'existe plus que des follicules P et A, état qui se maintient à 2,000 r, et la destruction est totale à 2,250 r.

Ainsi donc, une préparation par le prolan assure la stérilisation röntgenienne de l'ovaire à partir de 2,000 r et sa destruction à partir de 2,250 r. Par conséquent, l'hormone gonadotrope exerce le même office que le fractionnement et l'étalement de la dose; et ce fait très important indique déjà que le rendement meilleur obtenu par cette dernière technique par rapport à l'irradiation massive est dû à ce que la radio-sensibilité de l'organe, au cours des 5 jours sur lesquels s'étalent les séances d'irradiation, varie dans un sens *généralement croissant;* nous reviendrons ultérieurement sur cette constatation d'interprétation difficile.

c) *Lapines préparées par un radio-protecteur chimique*

On sait que parmi les amines expérimentées par BACQ et ses collaborateurs dans le but de découvrir une forme particulièrement efficace de radio-protecteur général, la β-mercapto-ethylamine occupe la toute première place.

L'action, très étendue, de cette amine s'est, jusqu'à présent manifestée avant tout sur le plan de la protection intégrale de l'organisme. Des efforts sont actuellement tentés dans le but d'étudier le mécanisme de cette protection, en partant de l'étude des réactions vis à vis des rayons röntgen, après intervention du protecteur, de certains organes, tissus ou cellules. Notons à ce point de vue, que BETZ et FRÜHLING (à propos du KCN), ont constaté que chez les souris protégées, les lésions radiologiques des organes hématopoïétiques sont identiques à celles des souris non protégées, mais que chez les premières la régénération myéloïde est rapide et considérable. ROSENTHAL, GOLDSCHMIDT et PICKERING ont fait avec la cystéine des observations comparables chez le rat. Et NEUKOMM et HERVE, dans un travail présenté au septième Congrès International de Radiologie et issu des Centres Anticancéreux de Lausanne et de Liège, aboutissent chez la souris à la même conclusion en ce qui concerne l'adéno-carcinome mammaire de Gaspari protégé par le Becaptan.

On voit donc l'intérêt que peut présenter une expérience de protection à l'égard d'un organe en place, aussi différencié et aussi endocrinologiquement dépendant que l'ovaire de lapine.

Or, il suffit de comparer sur notre schéma le comportement des ovaires irradiés chez des lapines protégées par le Becaptan ou le KCN avec celui des ovaires irradiés sans préparation pour se rendre compte de l'importance de la protection exercée par ces substances vis à vis des lésions radiologiques imposées aux follicules ovariens et plus particulièrement aux follicules primordiaux.

Considérons d'abord les prélèvements après délais longs. Par la technique d'irradiation massive nous ne sommes pas parvenu à stériliser l'ovaire. A 2,000 r environ — ce qui est normal — l'évolution folliculaire est encore complète; mais à partir de 2,250 r et jusqu'à la limite de 3.000 r, nous trouvons dans chaque ovaire, non seulement des follicules primordiaux mais encore quelques représentants du stade A. Et par la technique des fractionnements, nous obtenons exactement le même résultat, à cette différence près que la stérilisation et peut-être la destruction sont assurées à partir de 2,750 r. La conclusion qui ressort de cette expérience est évidemment que le protecteur a exercé son action sur nombre de follicules primordiaux au moment où ceux-ci étaient soumis à l'énergie radiante; et la conséquence tardive de cette protection est l'absence de stérilisation de l'ovaire irradié à dose massive jusqu'à 3,000 r (alors que sur la lapine normale, ce résultat est réalisé à 2,500 r), et sur le retard considérable apporté à cette stérilisation dans l'ovaire irradié à dose fractionnée (2,750 au lieu de 2,000 r).

Autre constatation de grand intérêt et qui cette fois découle de la comparaison des lectures d'ovaires prélevés — avec ou sans protection — après des délais courts: chez la lapine non protégée, l'ovaire prélevé après le 160e jours, est pour ainsi dire vide de follicules, quelle que soit la technique d'irradiation utilisée; les follicules comptés sont très rares et dépassent exceptionnellement le stade A (au moins à partir de 2,000 r); ceux (encore au stade P) qui évolueront plus tard sont dissimulés dans les mailles conjonctives et diastématiques du cortex ovarien. Au contraire, dans les ovaires protégés, l'activité folliculaire générale est élevée: sous dose massive, nous trouvons encore des follicules E ou F à 2,250 r, des follicules D à 2,500 r et des follicules A à 2,750 r, et sous dose étalée, des follicules D (atrétiques, il est vrai) à 2,000 r et des follicules A à 2,750 r.

Dès lors, nous pouvons affirmer que la protection s'exerce, si nous osons dire, à deux étages; elle soustrait complètement à l'action des rayons röntgen des follicules P qui confèreront à l'ovaire, tardivement, son visage habituel, et ne permet chez d'autres que des lésions radiologiques bénignes, qui ne les empêcheront pas de régénérer très rapidement.

S'il reste dans ce domaine beaucoup de choses à préciser, il est cepen-

dant permis d'affirmer que la protection chimique s'exerce au niveau de l'organite qu'est le follicule primordial; et comme celui-ci est dominé, dans son comportement général, par l'état fonctionnel de la cellule œuf, on doit supposer que c'est au niveau de celle-ci que s'exerce la protection qui, de ce fait, peut être créditée d'un caractère cellulaire.

Enfin, il est plus que probable que le seuil de protection, pour une cellule donnée, est proportionnel au seuil de radio-sensibilité: et comme celui-ci varie dans d'importantes limites d'un type cellulaire à un autre, il est aisé de comprendre la raison pour laquelle, dans nos expériences (DESAIVE, BACQ et HERVE) d'irradiation in toto de souris C 57 noires protégés par la Cystinamine (1,593 LABAZ), nous avons observé une régénération du tissu lymphoïde à côté d'une atrophie ovarienne complète; la dose utilisée (900 r sur le corps entier) a, dans ce cas particulier, largement dépassé la marge de protection de l'ovaire, sans atteindre celle du tissu lymphoïde.

Conclusions

Chez une lapine normale, l'appareil folliculaire de l'ovaire est détruit par une dose unique de 2,500 r; mais le fractionnement et l'étalement, sur cinq jours successifs, de la dose donnée de rayons röntgen, abaisse à 2,000 r la quantité d'énergie radiante nécessaire pour obtenir la stérilisation de la glande, c'est à dire l'incapacité définitive des follicules primordiaux à évoluer vers le type ovulatoire de de Graaf.

Cette constatation est en faveur de l'existence, au sein de la masse génératrice de follicules évolutifs que constitue la réserve ovarienne des follicules primordiaux, de variations importantes de la radio-sensibilité; la raison pour laquelle ces modifications, au cours des cinq jours sur lesquels s'étale l'irradiation fractionnée, se comportent de telle façon que leur résultante est un acroissement général de la radio-sensibilité folliculaire, dépend de facteurs biologiques dont nous publierons prochainement une analyse complète.

Pour mettre en évidence la variabilité de la sensibilité aux rayons röntgen des follicules ovariens (et plus particulièrement des follicules primordiaux) nous avons utilisé des lapines hypophyséoprives, gonadotropisées ou protégées par la β-mercapto-ethylamine.

L'hypophysectomie semble abaisser le seuil de stérilisation aux environs de 2,000 r; mais la durée relativement courte de nos observations (en raison de la viabilité réduite des animaux hypophyséoprives) ne nous permet pas d'être formel à ce sujet.

Par contre, la gonadotrophine chorionique abaisse à 2,000 r le seuil de stérilisation et à 2,250 r celui de la destruction folliculaire; et cette influence paraît être, dans une certaine mesure, proportionnelle à la quantité d'hormone utilisée.

Enfin, un radio-protecteur chimique efficace, comme la β-mercapto-ethylamine, relève considérablement ces deux seuils, puisque par la technique d'irradiation fractionnée, ceux-ci se situent à 2,750 r et que par la technique d'irradiation massive, ils ne sont pas atteints à 3,000 r.

Ces différentes observations sont en faveur, à la fois de la variabilité, sous diverses influences locales, régionales, ou générales de la radio-sensibilité de l'appareil folliculaire, et de l'intervention — au moins partielle — à l'échelle cellulaire, des radio-protecteurs chimiques.

RÉSUMÉ

Chez une lapine normale, il faut — dans des conditions expérimentales qui ont été choisies — une seule irradiation à 2,500 r pour obtenir la stérilisation de l'ovaire et, dans la majorité des cas, la destruction intégrale de l'appareil folliculaire. Le fractionnement de l'irradiation en 5 séances journalières successives de valeur égale abaisse le seuil de stérilisation à 2,000 r et celui de destruction à la limite de 2,250 r. La préparation de l'animal par des gonadotrophines, et dans une certaine mesure, la destruction, préalable à l'irradiation, de l'hypophyse donnent le même résultat.

Par contre, l'injection intraveineuse, immédiatement avant l'irradiation, d'un radio-protecteur tel que la β-mercapto-ethylamine, relève considérablement ces deux seuils qui passent à 2,750 r pour la stérilisation et à plus de 3,000 r pour la destruction. Il semble donc que la radio-sensibilité de l'appareil folliculaire varie, non seulement dans le temps, mais encore sous l'influence des altérations d'origine endocrinienne qui peuvent lui être artificiellement imposées. De plus, il est permis de considérer que l'action des radio-protecteurs chimiques s'exerce, tout au mois pour une part, à l'échelle cellulaire.

SUMMARY

Under given experimental conditions, a single irradiation dose of 2,500 r is required to obtain in the female rabbit sterilisation of the ovary and, in the majority of instances, complete destruction of the follicle apparatus. The fractionation of the irradiation into 5 equal consecutive daily sessions lowers the sterilisation threshold dose to 2,000 r and the dose for complete destruction to 2,250 r. The preliminary application of gonadotrophines to the animal and the previous destruction, to a certain degree, of the pituitary gland, give the same result.

On the other hand, intravenous injection, immediately before irradiation, of a 'radiation protective agent', such as β-mercapto-ethylamine, increases these two threshold doses considerably — to 2,750 r for sterilisation and to over 3,000 r for complete destruction. It appears, therefore, that the radiosensitivity of the follicle apparatus varies not only with the time factor, but also under the influence of endocrine changes which can be artificially produced. Furthermore, it is permissible to draw the conclusion that the chemical 'radiation protective agent' acts, to some extent at least, on a cellular level.

ZUSAMMENFASSUNG

Unter bestimmten experimentellen Bedingungen ist eine einzeitige Strahlendosis von 2,500 r notwendig, um bei einer weiblichen Ratte eine Sterilisation des Ovarium sowie, in der Mehrzahl der Fälle, eine völlige Zerstörung des Follikelapparates zu erreichen. Die Fraktionierung der Bestrahlung in 5 gleichförmige Bestrahlungen an aufeinander

folgenden Tagen verringert die Sterilisationsgrenzdosis auf 2.000 r und die Dosis für völlige Zerstörung auf 2.250 r. Die präliminäre Applikation von Gonadotropinen und die vorausgehende teilweise Zerstörung der Hypophyse der Tiere gaben das gleiche Resultat.

Andererseits erhöht die unmittelbar vor der Bestrahlung gegebene intravenöse Injektion eines »Strahlenschutzmittels« wie Beta-mercapto-ethylamin diese beiden Grenzdosen beträchtlich, nämlich auf 2.750 r für Sterilisation und auf über 3.000 r für völlige Zerstörung. Es scheint daher, als ob die Strahlenempfindlichkeit des Follikelapparates wechselt und zwar nicht nur mit dem Zeitfaktor, sondern auch unter dem Einfluss endokriner Veränderungen, die artificiell hervorgerufen werden können. Weiterhin ist es zulässig den Schlussatz zu ziehen, dass das chemische »Strahlenschutzmittel« in gewissem Ausmass zumindest auf einer cellulären Basis wirksam ist.

BIBLIOGRAPHIE

Bacq, Z. et Herve, A.: Protection chimique contre le rayonnement X. Bull. Acad. roy. de méd. de Belgique, VI[e] s. T. XVII (1952), 15.

Betz, H. et Früehling, L.: Etude de la régénération des organes hématopoïétiques chez les Souris irradiées à fortes doses et protégées par injection de KCN. C. R. S. biol. CXLIV (1950), 1013.

Desaive, P.: Contribution radio-biologique à l'étude de l'ovaire. Arch. Biol. LI (1940), 338.

— Contribution à l'étude du mécanisme de l'évolution et de l'involution folliculaire dans l'ovaire de Lapine adulte (2[e] partie) Arch. Biol. LIX (1948), fasc. 1.

— Contribution radio-biologique à la démonstration de la fixité, dans l'ovaire de Lapine adulte, des sources de développement folliculaire. Acta Neerlandica Morphologiae Normalis et Pathologicae IV (1941), 10.

Desaive, P., Bacq, Z. et Herve, A.: Causes de la stérilité des Souris femelles irradiées in toto et protégées par la cystéinamine. Experientia VIII (1952), 436.

Lamarque, P.: La restauration en radio-biologie. Presse méd. 60 (1952), 1039.

Lacassagne, A.: Effets histophysiologiques des rayons de Roentgen et de Becquerel Curie sur les tissus adultes normaux des animaux supérieurs. Radiophysiologie et Radiothérapie I (1927).

Lacassagne, A. et Nyka: Technique de destruction de l'hypophyse par le Radon. C. R. S. biol. 116 (1934), 581.

Neukomm, S. et Herve, A.: Communication personnelle d'une note présentée au 7[e] Congrès International de Radiologie.

Rosenthal, Goldschmidt et Pickering: Hematologic Changes in Rats protected by cysteine against body X irradiations. Am. J. Physiol. 166 (1951), 13.

BOOK REVIEW

DIE BEWEGUNGSBESTRAHLUNG. Von F. Wachsmann and G. Barth. 192 pages, 124 illustrations. George Thieme, Stuttgart 1953. DM 36: —.

The book under review is the first of its kind in which the various methods and techniques of moving field therapy are systematically presented and in which the possibilities as well as the limitations of the method are elucidated.

Following a well-written historical outline, an account is given in the first chapter of the development of moving field therapy and the basic principles of the technique. The significance of the focus—skin distance for the surface and depth dose, as well as the size of the field and above all the influence of its width upon the dose distribution in the object and its surroundings are made clear in tables and curves mostly based upon experimental investigations. Suitable forms of movement as well as the importance of the quality of the radiation and the dose rate are also discussed. It is pointed out that moving field therapy does not possess the disadvantages which appear in treatment with fixed fields and is shown, to be technically more simple. The method renders possible an intensive homogeneous irradiation of the object and a steep falling off of the dose in the surrounding parts which are thus spared. The authors consider that a half-value layer of 0.8 mm Cu is adequate for the radiation which is required for effective moving field therapy.

In the section which follows the authors describe rotation therapy, pendulum therapy and converging beam therapy with 200 kV apparatus as well as moving field therapy with ultra-hard rays.

In *rotation therapy*, the authors deal with the rotation of the patient around a vertical axis in the erect or sitting positions. It is pointed out that continuous screening is valuable for the control of the adjustment and of the reaction of the tumour. It appears to simplify the method especially if fixation of the patient is avoided. In this way and with the help of a remote controlled diaphragm, the adjustment time appears to be cut down to some few seconds. Regarding this it may be observed that rotation therapy carried out without careful immobilisation of the patient eliminates the possibility of keeping the tumour continuously in the rotation axis and a sufficiently precise determination of the main dosage is thus also precluded.

The width of field of not more than 4 cm proposed by the authors is, in the opinion of the reviewer, inadequate, for example, in cancer of the esophagus in which the result of the treatment would be better if a somewhat broader field were employed. It may also be pointed out in this connection that the penumbra plays a greater rôle in narrow than in broad fields.

For the indirect control of the tumour dose the authors utilize the exit dose, which is measured in the middle of the field and corrected for non-water-equivalent tissue. By such a method, information cannot, however, be obtained regarding the dosage of irradiation in the various parts surrounding the tumour and in which experience has shown quite large differences may exist. When the anatomic relations permit, the reviewer feels

that direct measurements in the region of the tumour with ionization chambers at several points along the axis of rotation should be carried out.

In order to make the employment of rotation therapy possible when the opportunity of measuring the exit dose does not exist, the authors have drawn up a table giving information about doses, which it is considered may constitute a certain guide. For those operators not trained in the problems of dosage, the table would appear to offer considerable hazards and risks of wrong dosage.

The information concerning the most suitable daily tumour dose is to a great extent in agreement with the experience of the reviewer. On the other hand, this does not concern the total tumour doses recommended for different types of tumours. Several of the upper limit values, for example, 8,000 r and 9,000 r in 8 to 10 weeks are set so high as to constitute a risk of radiation necrosis. These high doses may be viewed perhaps against the background of the above cited deficiences in treatment technique.

The authors raise the question as to whether the weekly dose may be given, for example in 3 instead of 5 or 6 sessions. They issue a warning against too great concentrations of the dose but have no definite personal experience on this matter.

In the section on the most important clinical indications, it is pointed out that the method is suitable in practise for tumours in all parts of the body. This section is verbose and definitely misleading for those without considerable radiotherapeutic experience. Above all it is worthy of note that the authors do not discuss any of their own material in detail in their dose recommendations and this in spite of the fact that it is stated earlier that they have already treated 500 patients with various forms of moving field therapy technique.

Pendulum therapy is carried out generally with the patient recumbent and well immobilised, a procedure described as constituting an undoubted advantage(!) over rotation therapy. The most important fact is, that according to the authors, the axis of the pendulum can be laid in the axis of every conceivable tumour in the body. The setting-up, however, takes longer.

There is a word of caution on selecting fields which are too small as it is then difficult to carry out exact adjustments. Those examples given in the book for the drawing up of the treatment technique are explicit and clear. The significance of the choice of pendulum angle, pendulum depth and size of field are presented clearly and illustrated with a number of curves. The dose distribution within a given tumour area can only be determined through phantom measurements. For tumours which can be covered in one field, the method appears to be very practicable and should in certain cases have definite advantages over the fixed field method. For larger tumours, the authors suggest several pendulum fields close to one another or a convergent curved field, which, however, make the estimation of the tumour dose particularly complicated and uncertain by reason of the distortions of the isodose curves.

The authors consider that the sphere of employment of pendulum therapy embraces in practice all tumours, with the exception of those of the skin, which are not too large.

In the chapter on *convergent beam therapy*, the Siemens-Reiniger convergent beam therapy apparatus is described in detail. With this apparatus, the convergent effect is obtained by the roentgen tube describing a spiral movement with a small rise along a spherical surface so that the central ray is directed the whole time to the centre of the sphere — the convergence point. In this way, a circular area of the skin receives a fairly uniform distribution of the surface dose, and at the same time the depth dose is relatively large. The plant is operated with constant voltage and filtration and with a suitable combination of diaphragms and applicators, and during every treatment the tube describes one complete spiral movement. The dose on the tumour thus depends only upon the dose rate and with the help of isodose-curves measured for 30 different combinations of applicators and diaphragms, an optimal adaption for every case of irradiation,

according to the authors, is possible. The sphere of employment of the method is stated to be so large that there is hardly any deep, moderately deep or surface tumour which cannot be better treated by convergent beam therapy than by crossfire technique. In the opinion of the reviewer this new technique of irradiation upon but a single field of treatment imposes very great demands for precise information regarding the situation and extent of the tumour as well as upon the possibilities of reproducing the adjustment technique. As only tumours of a diameter less than about 5 cm can be homogeneously irradiated through one field, multiple field irradiation is recommended for larger tumours. The planning of convergent beam therapy for several fields however, is, according to the authors, very difficult and in order to facilitate treatment they give suitable combinations for various tumour situations.

All this is supported only by theoretical calculations and not upon clinical experience. To this must be added that the prepared isodose-diagrams can only be used for a small number of tumours without corrections for curvatures of the surface of the body, for varying absorption in non-water-equivalent tissue and for volumes of different bodies. Such corrections complicate the determination of the dose and under certain conditions errors may become fairly large, especially when several fields are used.

Moving field therapy with ultra-hard rays, which up to now has only been employed in England and America, affords the possibility, according to the authors, of optimal dose distribution in the irradiation of a deep-seated object. They point out, that the optimal energy in the irradiation of human tumours with ultra-hard rays lies where the exit is the same as the entrance dose, that is to say, between 12 and 15 MeV. An advantage of ultra-hard radiation over roentgen therapy at 200 kV lies in the fact that the side scatter is insignificant and the size of the field has less influence upon the depth dose. Furthermore the absorption differences also fall away almost entirely in the various tissues. The authors describe the apparatus constructed up to now for moving field therapy with ultra-hard rays and at the same time point out that so-called horizontal rotation with the patient recumbent and the radiation directed obliquely produces the best distribution between the tumour and skin doses.

This form of therapy is held to be superior to every other kind of moving field therapy if only by reason of the very much simpler estimation of the dose and physical advantages wholly justifying the use of the method. Over and above that, clinical experiences are stated to be favourable.

The authors have made a creditable attempt to popularize the various methods of moving field therapy. The book is well worth reading when it deals with the technical and physical factors and presents a complete conception of the theoretical foundations. The more, therefore, is one forced to complain that the clinical sections are verbose, full of reiterations and contain misleading or erroneous information especially concerning the total tumour doses recommended. Above all, one is surprised by the assertion that following the treatment, adequately carried out, of a tumour, 60 % of the dose administered may be repeated in 6 months, 80 % in 9 months and 100 % in one year. This is contrary to all experience.

So long as clinical trials remain incomplete, the place of moving field therapy rests only in the larger radiotherapeutic clinics where physical assistance is available.

Martin Lindgren.